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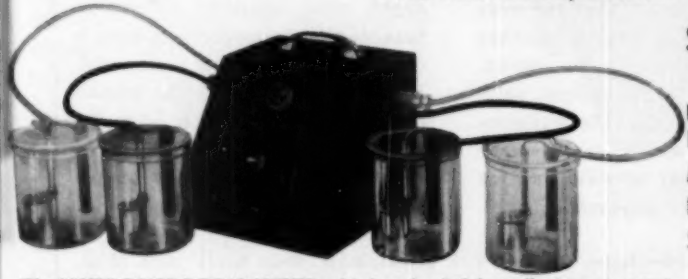

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CONTENTS

PAGE

Medicolegal Identification of Seminal Stains Using the Acid Phosphatase Test. Frank Lundquist, Ph.D., Copenhagen, Denmark.. 395

Polycystic Kidney (Mesonephros) in the Goldfish. Hans G. Schlumberger, M.D., Columbus, Ohio..... 400

Metabolite Antagonists in Experimental Cancer: Guanazolo. Boris Sokoloff, M.D., Ph.D.; James B. Redd, Ph.D., and Raymond Dutcher, B.S., Lakeland, Fla..... 411

Studies on the Effect of Radioactive Colloidal Gold on the Development of the Oral Structures of the Mouse. M. S. Burstone, D.D.S., Chicago 419

Nonspecific Periappendical Granulomas. James E. Musgrove, M.D., and Malcolm B. Dockerty, M.D., Rochester, Minn..... 427

Pathology of Early Amebic Hepatitis: An Experimental Study. G. M. Carrera, M.D., New Orleans..... 440

Varicella Pneumonitis: Report of a Case with Autopsy Observations. Lester Frank, M.D., Burlington, Vt..... 450

CASE REPORTS:

A Partially Healed Primary Lesion in a Case of Generalized Histoplasmosis. Dale M. Schulz, M.D., St. Louis..... 457

Aortic Atresia, Mitral Stenosis, Hypoplasia of the Left Ventricle and Other Cardiac Anomalies in Newborn. James A. Gunn, M.D., and John B. Miale, M.D., Marshfield, Wis..... 464

Adrenal Cysts. J. Zuckner, M.D., St. Louis..... 468

GENERAL REVIEWS:

Pathology of Oxyuriasis with Special Reference to Granulomas Due to the Presence of Oxyuris Vermicularis (Enterobius Vermicularis) and Its Ova in the Tissues. W. St. C. Symmers, M.D., M.R.C.P., Birmingham, England..... 475

NEWS AND NOTES 517

BOOKS RECEIVED 518

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MEDICOLEGAL IDENTIFICATION OF SEMINAL STAINS USING THE ACID PHOSPHATASE TEST

FRANK LUNDQUIST, Ph.D.
COPENHAGEN, DENMARK

THE PRESENCE of semen or seminal stains constitutes important evidence in cases of sexual crime, and in many cases the only objective evidence. It is therefore of great importance to have available methods by which the presence of semen can be definitely ascertained. As Pollak [1] in 1943 published a comprehensive review of the identification of semen and seminal stains, it is considered unnecessary here to describe the older methods to any great extent.

A number of chemical tests have been claimed by their inventors to be specific for semen, but closer investigation has always shown this not to be true. Some of the tests may be very useful, but none of them singly provides proof that the stain in question contains semen. Among the more useful methods may be mentioned Florence's test, which depends on the high concentration of choline in semen. Free choline does generally not occur in other products in very high concentrations, whereas in semen concentrations of about 200 to 300 mg. per 100 cc. are normal.[2] Choline is formed by the rapid enzymatic splitting of phosphoryl choline, which originates from the vesicular glands. Other tests of some practical value are based on the fact that spermine and spermidine occur in considerable amounts in human semen.

The only method which has been considered to prove that semen is present in a stain has until quite recently been the microscopic demonstration of intact spermatozoa. In a number of cases it may, however, be impossible or very difficult to find spermatozoa on the effects in question for the following reasons.

1. The person from whom the suspect stain originates may be suffering from aspermia (absence of spermatozoa in the ejaculate). This condition is far from being rare; some authors even claim that about 10 per cent of the male population suffer from this condition. Among sexual criminals it is perhaps not unreasonable to expect aspermia to

From the University Institute of Legal Medicine.

1. Pollak, O. J.: Arch. Path. **35**:140, 1943.
2. Lundquist, F.: Acta physiol. Scandinav. **13**:322, 1947.

a higher extent than in the population at large, because of the presumably higher frequency of venereal diseases, which may cause aspermia. Another cause of aspermia which in some countries cannot be disregarded is surgical vasectomy performed on feebleminded persons.

2. The stain may consist of a part of the ejaculate which does not contain spermatozoa. It is known that spermatozoa are not present to an equal extent in the various parts of the ejaculate; e. g., pure prostatic secretion is often expelled before vesicular gland secretion and sperm. The first fraction of the ejaculate is generally expelled with considerable force and can be imagined in some cases to give rise to stains removed quite a distance from those due to the rest of the ejaculate. The last part of an ejaculate may likewise be poor in spermatozoa, consisting often of nearly pure vesicular gland secretion.

3. If the stain examined is formed by filtering of seminal fluid through several layers of cloth, the spermatozoa (especially in cases of oligospermia) may be retained completely or nearly so by the first layer or layers. This phenomenon has been observed several times in the laboratory with which I am associated.

It appears highly desirable to have a specific test which is not dependent on the demonstration of spermatozoa. The chemical composition of human semen presents some rather unique features, among which the high concentrations of choline and spermine have already been mentioned. The concentration of citrate is high, too, but it appears doubtful whether this substance is suitable as a characteristic of semen. Other products contain citric acid in large amounts (e. g., milk and fruit), and this fact alone would render the test unspecific. The same is true of fructose, the sugar found in semen in large amounts.

In 1945 the demonstration of phosphatase, which is present in prostatic secretion in tremendous amounts, was proposed as a specific test for semen.[3] In Denmark three investigators simultaneously worked on the problem, and all came to the conclusion that the determination of the acid phosphatase content of stains may be used as a specific test for the presence of semen.

Hansen[4] constructed a simple apparatus for extraction of stains occurring on textiles. A measured volume of water is flushed back and forth through a well defined area of the stained cloth to be examined. In this way effective extraction is completed in a very short time without destroying the textile. The phosphatase content of the stain is expressed as phosphatase units per square centimeter. If the number of units is above a certain critical value, it can be stated with certainty that the stain in question contains semen. In practice it is hardly ever

3. Lundquist, F.: Nord. med. **28**:2131, 1945.

4. Hansen, P. F.: Acta path. et microbiol. Scandinav. **23**:187, 1946.

necessary to make an actual measurement of the phosphatase content, for under the conditions used in the assay the color developed with phenol reagent will be as dark as ink if semen is present and very faint in all other cases. (Phenyl phosphate is used as a substrate and 0.25 cc. of extract is incubated with 10 cc. of buffer substrate solution for 15 minutes.)

A modification of Hansen's flushing syringe was described by Carpenter and Watson.[5] Their device appears to be an improvement as compared with the more simple original apparatus.

Riisfeldt [6] described extraction, in a standard volume of water, of tiny bits (3 mm. in diameter) of the stained textile, cut out with the help of a leather punch. From the phosphatase concentration of the extract, the thickness of the textile and the character of the cloth the approximate phosphatase concentration of the fluid which gave rise to the stain under examination may be calculated.

Rasmussen [7] employed the dry weight of the substance extracted as a basis for expressing the phosphatase content. All these three authors have made a careful examination of the phosphatase content of a large number of products which might conceivably be met with in stains. In no case was a phosphatase concentration comparable to that of human semen encountered. This result has recently been confirmed by Kaye,[8] who examined a number of food products and body fluids.

In the laboratory of the University Institute of Legal Medicine, in Copenhagen, we have used the phosphatase test in medicolegal cases for nearly six years and have found it to be very useful indeed. During the first three or four years we made examinations for both spermatozoa and phosphatase in every legal case. Later on, when it was established how often the phosphatase test is negative even though spermatozoa are present, only those effects were subject to the phosphatase test which did not show the presence of spermatozoa at the first, preliminary examination. The following procedure was employed as a routine: The effect is examined in ultraviolet rays, and the fluorescent areas are marked. The areas thus indicated are examined for the presence of spermatozoa by making preparations of threads isolated from the textile. The effects are then examined for phosphatase according to the procedure of Hansen.[4]

Clothes, sheets, rugs and other effects from 346 legal cases involving various sexual crimes have so far been examined for phosphatase. Each one of these cases includes a number of effects with several individual stains, which were extracted and tested. More than 2,000 stains have been examined by this method.

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5. Carpenter, E. D., and Watson, E. M.: Canad. J. M. Technol. **9**:1, 1947.
6. Riisfeldt, O.: Acta path. et microbiol. Scandinav., 1946, supp. 58.
7. Rasmussen, M. P. S.: Ann. de méd. lég. **25**:109, 1945.
8. Kaye, Sidney: J. Lab. & Clin. Med. **34**:728, 1949.

A short report of the first 140 legal cases, in which both microscopic and biochemical examinations were made, was published in 1948.[9] In 49 of the cases spermatozoa were found. In 8 of these cases with positive microscopic evidence the phosphatase test was negative. In two cases the stains in question were more than half a year old, and it has been shown experimentally that the phosphatase content of stains on textiles may diminish to a low level when the textiles are stored for six months under ordinary room conditions. In two other cases the major parts of the stains had been cut away for determination of the blood group before the phosphatase determination could be made. In two cases phosphatase levels just below the critical were encountered, and in the remaining two no phosphatase at all could be detected. Riisfeldt has

TABLE 1.—*One Hundred and Forty Cases in Which Examinations for Both Spermatozoa and Phosphatase Were Made*

	Spermatozoa Present	Spermatozoa Absent
Phosphatase present	41	9
Phosphatase absent	8	82

TABLE 2.—*Two Hundred and Six Cases in Which Spermatozoa Were Not Found by Preliminary Examination*

	Spermatozoa Absent	Spermatozoa Demonstrated on Renewed Examination
Phosphatase present	12	20
Phosphatase absent	174	Not examined

observed that in certain cases chemical substances from the textiles may destroy the phosphatase, and it is also known that subjects suffering from chronic prostatitis sometimes have low levels of acid phosphatase in the semen.

In 9 cases phosphatase was found at high levels even though spermatozoa could not be demonstrated, despite careful attempts.

In the subsequent 206 cases spermatozoa were not demonstrated in the preliminary examination of the effects in question. In 32 of these a clearly positive phosphatase reaction was found. The search for sperm was repeated scrupulously and was successful in 20 of the cases, leaving 12 seminal stains, in which spermatozoa could not be demonstrated though several different methods of preparation and staining were employed. In three of these 12 cases spermatozoa had been found on other effects belonging to the same case. Conceivably one has to do here with groups 2 and 3, listed above. Tables 1 and 2 sum-

9. Lundquist, F.: Acta med. legal. et soc. **1**:1948.

marize our experiences with the phosphatase test for demonstration of seminal stains.

By employing this new method it has been possible in 21 legal cases to prove that suspect stains were actually caused by semen, although spermatozoa could not, despite the utmost care, be demonstrated. In the light of the extensive investigations quoted [10] we do not hesitate to consider the positive phosphatase test a proof of the presence of semen as valid as the demonstration of spermatozoa. In our opinion it is probable that subjects suffering from aspermia have been responsible in a considerable number of these cases. However, we have not been able to verify this assumption as yet.

The phosphatase test cannot replace the microscopic examination of seminal stains for a number of reasons, among which may be mentioned that old stains show little or no phosphatase activity and that certain chemicals used in the treatment of textiles may prevent the test. It appears, however, that the test provides an excellent supplement to the classic method in either of the modifications mentioned, and it would appear improbable that any seminal stain should remain unrecognized when both these methods are used.

SUMMARY

The phosphatase test for detecting seminal stains in legal cases of sexual crime has been employed in medicolegal practice during six years. The results of 346 such cases are briefly reported. Twenty-one cases were encountered in which the presence of semen was proved by the phosphatase test, though no sperm could be found. It is concluded that the microscopic and the biochemical examination of stains for the presence of semen supplement each other excellently.

10. Hansen.[4] Riisfeldt.[6] Rasmussen.[7] Kaye.[8]

POLYCYSTIC KIDNEY (MESONEPHROS) IN THE GOLDFISH

HANS G. SCHLUMBERGER, M.D.
COLUMBUS, OHIO

PHYSIOLOGISTS have carried out extensive studies of renal physiology on fish, but pathologists have seldom had the opportunity to investigate diseased or otherwise abnormal kidneys of these animals. Protozoan and metazoan parasites, as well as fungi, have been reported in the kidneys of fish by zoologists, but the effects of these infestations on the host have been slighted. One of the best, although brief, discussions of renal diseases occurring in fish is given by Plehn in her guide to diseases of fish.[1]

The polycystic kidneys of man have presented an intriguing problem in pathogenesis, well reviewed recently by several authors.[2] Interest in the condition has been heightened by the knowledge that in many instances a hereditary factor is present.[3] The spontaneous occurrence of this abnormality in the goldfish (Carassius auratus) provides an opportunity to compare the changes produced as they affect the structure and the function of the mesonephros in a fresh water fish with the changes observed in the metanephros of man.

MATERIAL

It was observed that about 5 per cent of the goldfish in a large urban pond bear cutaneous neurofibromas. This stimulated closer inspection of the fish and led to finding 11 with polycystic kidneys; of these, three also had the skin tumors. In another outdoor pond 150 miles (240 kilometers) from the first it was possible to select four goldfish from among several hundred as having polycystic kidneys on the basis of their swollen abdomens. These four fish were used in the studies of renal function detailed below; in each instance the diagnosis was confirmed at autopsy. The affected fish were equally distributed according to sex.

From the Department of Pathology, Ohio State University College of Medicine.

Read at the meeting of the American Society for Experimental Pathology in Atlantic City, N. J., April 18, 1950.

This investigation was supported in part by a research grant from the National Cancer Institute, of the National Institutes of Health, Public Health Service.

1. Plehn, Marianne: Praktikum der Fischkrankheiten, Stuttgart, Schweizbart, 1924.

2. (*a*) Norris, R. F., and Herman, L.: J. Urol. **46**:147, 1941. (*b*) Lambert, P. P.: Arch. Path. **44**:34, 1947. (*c*) Rall, J. E., and Odel, H. M.: Am. J. M. Sc. **218**:399, 1949.

3. Cannon, J. F.: Ann. Int. Med. **27**:610, 1947.

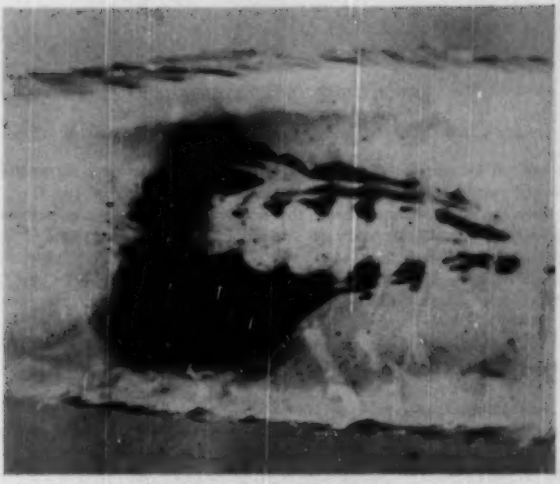

Fig. 1.—Normal goldfish kidneys in situ. The anterior abdominal wall has been cut away, and the triangular kidneys are seen lying retroperitoneally on either side of the vertebrae. The proximal (cephalic) ends are fused. The kidney in the upper portion of the figure appears smaller as the result of foreshortening. Natural size.

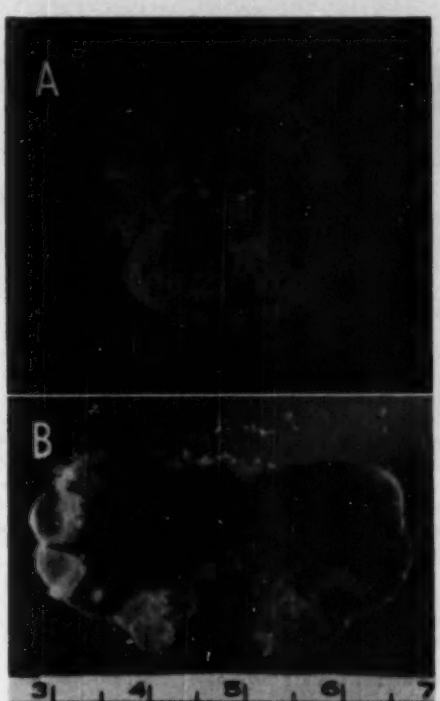

Fig. 2.—*A*, excised kidney bearing many 0.3 to 2 mm., thin-walled cysts. The other kidney of this fish showed similar changes. Twice natural size.
B, isolated kidneys bearing several 5 mm. cysts within the renal substance and along the lateral margin.

GROSS PATHOLOGIC OBSERVATIONS

The normal kidneys of the goldfish are flat, triangular organs, paravertebral in position and joined anteriorly by a broad isthmus of renal tissue (fig. 1). Structurally they represent a mesonephros; the metanephros found in mammals does not develop in fish. Small cysts scattered throughout the renal substance (fig. 2 *A*) or arranged along the lateral margins (fig. 2 *B*) do not greatly alter the contour of these organs.

Goldfish with large renal cysts show an extraordinary abdominal distention (fig. 3), often associated with some loss in agility. In one instance the great collection of fluid in the cysts interfered with the buoyancy of the animal; only continuous active swimming movements prevented it from sinking at once to the bottom of the tank.

On dissection the large cysts are found to extend ventrally over the swim bladder and to encroach on the celomic cavity, compressing liver, gonads and intestine (fig. 4 *A*). In one fish each lateral half of the celom was filled by an extremely thin-walled, multiloculated cyst, measuring 8 cm. in diameter (fig. 4 *B*). The ovaries had been reduced to narrow ribbons intimately fused with the cysts; careful

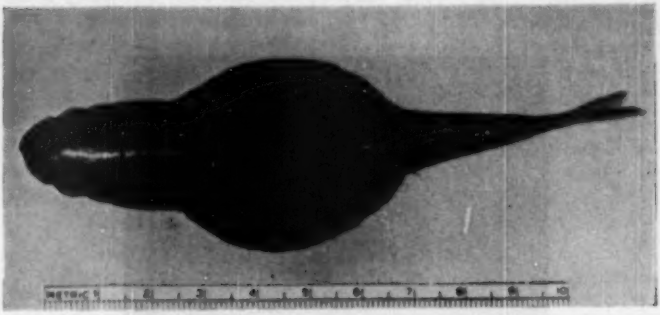

Fig. 3.—Dorsal aspect of a goldfish with polycystic kidneys, showing distention of the abdomen.

gross and microscopic examination was needed to demonstrate that the cysts were of renal and not ovarian origin.

Kidneys with multiple cysts measuring 0.5 to 2.0 mm. in diameter were placed in 35 per cent hydrochloric acid after being fixed in 4 per cent formaldehdye. After 24 hours in the acid they were washed in running water. Under a binocular dissecting microscope, the cysts and adjacent structures were then teased free. The great majority of cysts examined in this manner are found to be thin-walled spheres; in the wall of each is a minute nodule, the glomerulus. Rarely there is a fusiform dilatation in the course of a tubule, although no obstruction can be recognized elsewhere in the nephron.

HISTOPATHOLOGIC ASPECTS

The normal histology of the fish kidney has recently been reinvestigated by Edwards.[4] The glomerulus of the goldfish, unlike that of some other types of fish,

4. (*a*) Edwards, J. G.: Am. J. Anat. **53**:55, 1933; (*b*) Anat. Rec. **63**:263, 1935. Rec. **63**:263, 1935.

is well developed and larger than that in the reptilian or the avian kidney.[4a] The nephric tubule is composed of a very short neck segment, a proximal convolution, an intermediate segment, a distal convolution and a collecting duct. In the goldfish, as in many other teleosts, the kidney is also the chief site of hemopoiesis.[5] Large

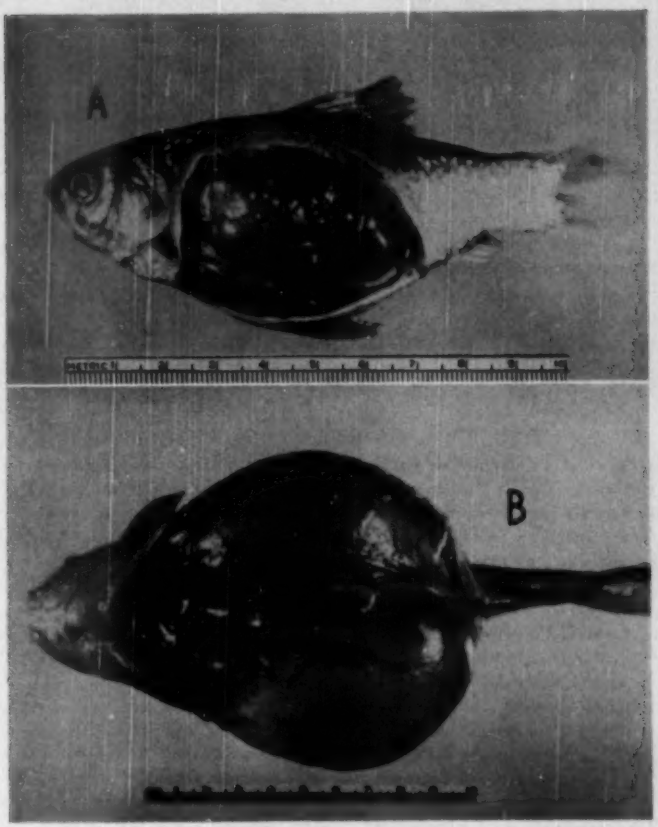

Fig. 4.—*A*, same animal as that in figure 3. The upper two thirds and the entire length of the celomic cavity is replaced by the polycystic kidney. The liver, the testis and the intestine occupy a narrow band below the kidney. The degree of involvement is equal on the two sides. The fish is listed as no. 1 among those with polycystic kidneys in table 1. It is representative of the four goldfish used in the renal function studies.

B, another goldfish with each kidney replaced by huge, multiloculated, thin-walled cysts. The ovaries, the intestine and the liver are reduced to a flat ribbon in the midline of the abdomen.

5. Jordan, H. E.: Comparative Hematology, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938.

collections of immature erythrocytes, leukocytes and hemosiderin-containing macrophages are present between the nephrons. Many parasitic worms are found. These are often encysted in, or encapsulated by, host connective tissue and usually are wholly or partly calcified. Examination of multiple sections and of teased preparations fails to demonstrate tubular obstruction that can be attributed to these parasites, nor is there evidence of acute or chronic inflammation.

Bowman's capsule is normally closely applied to the glomerular tuft; only a narrow subcapsular space separates the visceral and the parietal epithelium (fig. 5 *A*). The cysts represent a dilatation of the subcapsular space. They have a thin connective tissue wall and are lined by the flat squamous epithelium of Bowman's capsule. As the cysts grow the subcapsular space becomes progressively larger (figs. 5 *B* and 6). In each of these cysts, serial sections reveal a glomerular tuft attached to the wall and often apparently still functioning, to judge by the erythrocytes present in the capillaries. Stained preparations often show a pink granular material within the cysts.

The absence of a patent communication between the cyst and the tubular portion of the nephron, first revealed in the teased preparations, is supported by examination of serial sections; in none is union with a tubule demonstrable. Occasionally in the involved kidney there may be an associated tubular dilatation, which in rare instances approaches cystic proportions (fig. 7).

RENAL FUNCTION

Most of the nitrogenous wastes excreted by fish are eliminated through the gills rather than the kidneys. This was convincingly demonstrated by Homer Smith,[6] who found that the branchial excretion consists largely of the readily diffusible substances, ammonia, urea and amine derivatives. The less diffusible products, viz., creatine, creatinine and uric acid, are eliminated by the kidneys. Approximately 6 to 10 times as much nitrogen is excreted in the same interval by the gills as by the kidneys.

Four goldfish with massive polycystic kidneys (fig. 4 *A*) and four normal controls were tested. Each fish was slipped tail first into a thin-walled rubber sac, the lips of which fitted snugly about the trunk at the level of the pectoral fins. The urine was collected in this sac. The method was successfully used by Meyer[7] in his study of chloride balance in the goldfish. Intestinal contents and skin secretions that contaminate the sample add only a negligible amount of nitrogen to it.[6] The fish was then placed in a glass jar with a measured amount of water, usually about 200 cc., and the water was continuously aerated by compressed air. Aeration was necessitated by the small amount of water used—about 2 cc. per gram of fish. The p_H of the water was 7.0 to 6.8; therefore, the aeration did not carry off any ammonia nitrogen.

Each experiment was continued for 20 to 23 hours. At the end of that time the volumes of water and urine were measured and nonprotein nitrogen determinations

6. Smith, H. W.: J. Biol. Chem. **81**:727, 1929.

7. Meyer, D. K.: Science **108**:305, 1948.

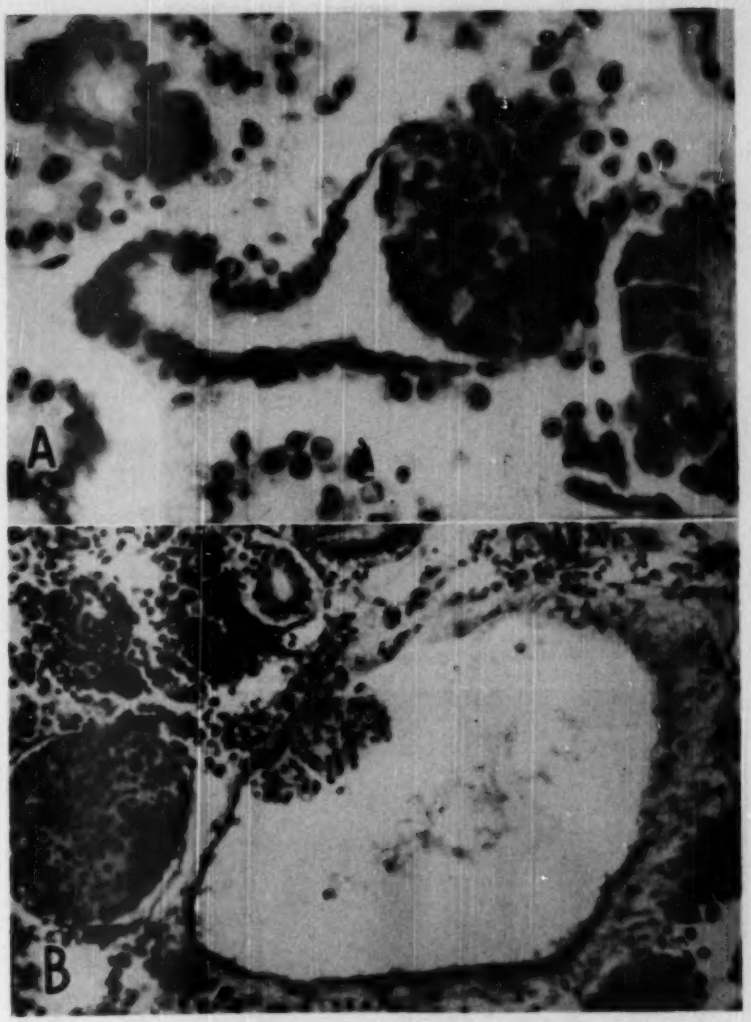

Fig. 5.—*A*, normal glomerulus of a goldfish kidney. The narrow neck segment joins the subcapsular space to the wider proximal convoluted tubule. The long cilia that fill the lumen in the neck segment are not shown. Hematoxylin and eosin stain; × 240.

B, small glomerular cyst showing distended subcapsular space and the glomerular tuft with patent capillaries. The thin connective tissue wall of the cyst is lined by pavement epithelium. Hematoxylin and eosin stain; × 135.

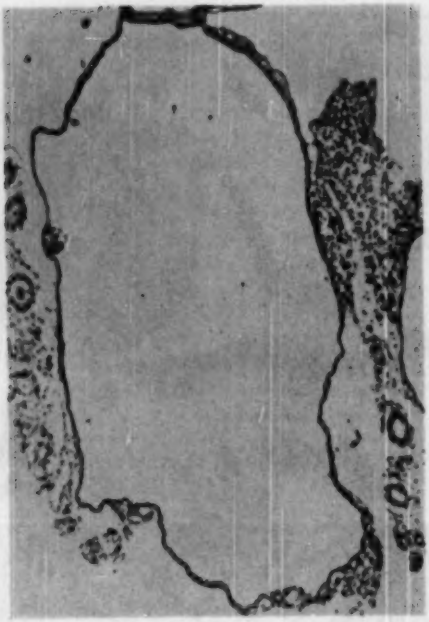

Fig. 6.—Later stage in the development of a glomerular cyst, showing a small capillary tuft still attached to the wall. Hematoxylin and eosin stain; × 90.

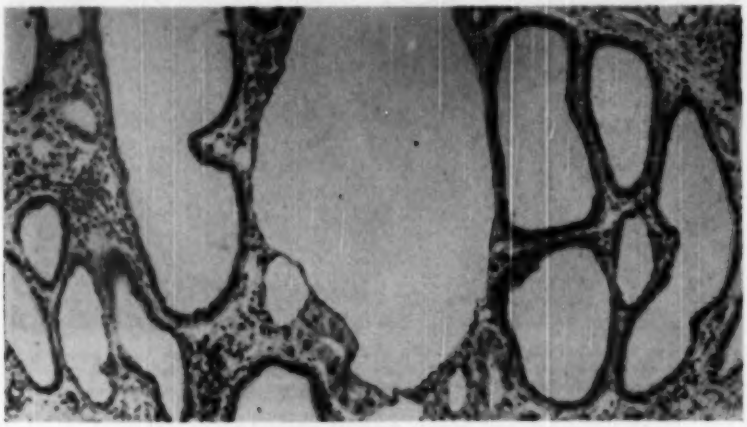

Fig. 7.—Dilated tubules occasionally found in polycystic kidneys of the goldfish. Hematoxylin and eosin stain; × 125.

run on each. The results (table 1) indicate that approximately 85 per cent of protein breakdown products are excreted by the gills and 15 per cent by the kidneys in healthy goldfish. In fish with polycystic kidneys renal function accounted for only 9 per cent of the total nitrogen eliminated. Although the series is small, the results are consistent. The possibility that the fish may establish at least temporary equilibrium is indicated by the nearly identical amounts of nitrogen excreted by polycystic kidney fish 2 when first tested (table 1, 2 A) and again two weeks later (table 1, 2 B).

TABLE 1.—*Branchial and Renal Nitrogen Excretion in the Goldfish*

			Water		Urine		NPN* Excreted	
Fish No.	Wt., Gm.	Time, Hr.	Vol., Cc.	NPN,* Mg.	Vol., Cc.	NPN,* Mg.	% by Gills	% by Kidneys
			Controls					
1	40	17	470	7.0	6.0	1.3	84.34	15.66
2	103	22	250	11.5	35.0	2.6	81.55	18.45
3	122	23	270	13.5	9.0	1.8	88.24	11.76
4	104	23	170	10.6	6.5	1.7	86.18	13.82
						Mean	85.08	14.92
						Stand. dev. ± 2.34		
			Fish with Polycystic Kidney					
1	51	23	185	6.5	3.0	0.57	91.94	8.06
2A	91	23	180	9.0	5.0	0.75	92.31	7.69
2B	100	23	170	6.9	2.5	0.57	92.37	7.63
3	147	20	175	5.7	1.5	0.56	90.77	9.23
4	47	23	165	5.6	1.3	0.78	88.15	11.85
						Mean	91.11	8.89
						Stand. dev. ± 1.77		

* NPN indicates nonprotein nitrogen.

TABLE 2.—*Nitrogen Content of Blood, Urine and Cyst Fluid in Goldfish with Polycystic Kidneys*

		Blood		Urine		Cyst Fluid	
Fish No.	Wt., Gm.	Vol., Cc.	BUN,* Mg. per 100 Cc.	Vol., Cc.	NPN,* Mg. per 100 Cc.	Vol., Cc.	NPN,* Mg. per 100 Cc.
1	51	0.3	5.6	3.0	19.0	0.5	10.1
2A	91	1.0	3.5	5.0	15.0	3.0	9.0
2B	100	0.5	2.5	2.5	22.8	1.5	16.5
3	147	0.3	3.1	1.5	28.6	6.0	11.2
4	47	...	...	1.3	60.0	2.5	18.5

* BUN indicates blood urea nitrogen; NPN, nonprotein nitrogen.

For several of the fish with polycystic kidneys a blood urea nitrogen determination was made on blood obtained from the heart. The values ranged from 2.5 to 5.6 mg. per 100 cc. (table 2). Two similar determinations made on normal fish gave 2.25 and 2.50 mg., respectively, indicating slight if any retention of nitrogen in the fish with abnormal kidneys. This may be attributed to the branchial excretion of these substances.

Lambert [2b] has shown that in human beings with polycystic kidneys the concentration of urea is 7 to 14 times as great in the bladder urine as in the cyst fluid. In the goldfish the concentration of nitrogen in the urine is only 2 to 3 times greater

than that in the cyst fluid (table 2). This may be attributed to the fact that the fish kidney is normally unable to excrete a hypertonic and hence very concentrated urine.[8]

The volume of urine excreted by the fish with polycystic kidneys averaged only half that eliminated by the normal controls (table 1). Yet, neither edema nor anasarca was ever observed in these animals, although water retention does occur in fish. I have seen extreme edema of the subcutaneous tissues and marked ascites in goldfish dying as the result of Pseudomonas hydrophilus septicemia. In none of these, however, was there an associated polycystic abnormality of the kidneys.

COMMENT

The only mention of polycystic kidneys in fish that could be found in the literature was made by Plehn,[1] who included a photograph of the lesion in a carp—a species closely related to the goldfish. She suggested that it is not uncommon among carp and that it may be due to ureteral obstruction. No evidence of such obstruction is given.

The only other report of renal cysts in fish was made by Grafflin,[9] who noted small cystic spaces within the glomerular tufts of lungfish, marine teleosts, amphibians, reptiles and birds. These "cysts" are wholly different from the glomerular cysts of the goldfish. A structure similar to that described by Grafflin was seen in the polycystic kidneys of a goldfish; apparently it represents a localized vascular ectasia within the glomerular tuft.

The pathogenesis of the polycystic changes in the goldfish kidney cannot be determined with certainty. The short neck segment that joins the glomerular capsule with the proximal convoluted tubule is normally narrow and its lumen almost occluded by the long cilia of its epithelial lining cells.[4a] The very high incidence of glomerular cysts in the polycystic goldfish kidney suggests that during embryogenesis the narrow neck segment may have become wholly occluded either by a fault in morphogenesis or as the result of an inflammatory process of which all trace has disappeared in the adult fish. It should be noted that the goldfish kidney continues to grow and differentiate after the animal has hatched and while it is exposed to all the vicissitudes of its external environment. Writing of the human kidney, Norris and Herman [7a] suggest that slight abnormal constrictions in the growing nephron may facilitate the development of proximal cystic dilatations.

Failure of the nephrons and collecting tubules to unite during development of the metanephros has long been suggested as the cause of polycystic kidneys in man. The permanent kidney of the fish is a mesonephros, and hence there is no ureteric blastema with its derivative collecting tubules. However, in the mesonephros the distal convoluted

8. Smith, H. W.: Quart. Rev. Biol. **7**:1, 1932.

9. Grafflin, A. L.: Biol. Bull. **72**:247, 1937; Anat. Rec. **74**:147, 1939.

tubules fuse with, and empty into, the mesonephric duct.[10] Should this fusion fail, cyst formation might occur. But occlusion of the tubules at their distal ends can hardly account for the blind glomerular cysts that characterize the polycystic kidney of the goldfish.

Kampmeier [11] has shown that in the metanephros the first generation of uriniferous tubules is vestigial. The next two or three generations, though normally laid down and joined to their collecting ducts, persist only for a time and degenerate during later fetal stages. Subsequently McKenna and Kampmeier [12] offered the hypothesis that in man polycystic kidneys result when these early generations of nephrons persist and become cystic after losing their connection with the collecting tubules. This explanation is not applicable in the case of the goldfish, in which secondary degeneration of some of the nephrons following fusion with the mesonephric duct is not a feature of normal morphogenesis.[10]

The polycystic kidney of the goldfish resembles that of man, particularly that of the newborn, in which glomerular cysts are numerous. Here, too, as in the fish, but unlike the condition in adults, cystic nephrons are always separated from their excretory tubules.[2b] Unlike the human infant, the fish with polycystic kidneys of this type may live for several years. This may be attributed to subtotal involvement of the kidneys and to the excretion of protein wastes by the gills.

Because the goldfish can eliminate up to 90 per cent of its nitrogenous wastes through the gills, renal failure alone will not produce azotemia. Indeed, most so-called artificial kidneys now being used in the treatment of acute renal insufficiency in man could more accurately be named "artificial gills," since their structure and function closely resemble that of the branchial organs of the fresh water fish.

An upset in its water balance is a continuous threat to the goldfish. Because the blood and tissue fluids are hypertonic to the surrounding water, there is a constant ingress of water through the gills [9] and intestinal mucosa.[13] Using the thorotrast[9] (colloidal thorium dioxide) technic of Frank and Allee,[13] I found a remarkable range in the speed and the degree of concentration of the radiopaque colloidal thorium dioxide by the intestinal tract of the healthy goldfish. The possibility exists, therefore, that water balance is achieved in fish with polycystic kidneys by a great reduction of the intestinal absorption of water swallowed during feeding. However, the small amount of fluid collected

10. Felix, W.: Die Entwickelung der Harnorgane, in Hertwig, O.: Handbuch der vergleichenden und experimentellen Entwicklungslehre des Menschen und der Wirbeltiere, Jena, Gustav Fischer, 1906.

11. Kampmeier, O. F.: Anat. Rec. **33**:115, 1926.

12. McKenna, C. M., and Kampmeier, O. F.: J. Urol. **32**:37, 1934.

13. Frank, P., and Allee, W. C.: Physiol. Zoöl. **23**:134, 1950.

in the rubber sac, which includes both urine and intestinal contents, does not support this view and indicates rather that the intake of water is diminished by a decrease of the amount swallowed or of the amount absorbed by the gills. The latter are probably the chief source of water uptake in the fresh water fish.[8] Furthermore, it has been shown that chlorides and sodium can be absorbed or excreted against an osmotic gradient by the gills.[14] However, decreased branchial absorption of water before there is systemic edema due to renal failure cannot be demonstrated from available data. Finally, the cysts themselves, particularly when they have become massive (fig. 4), may represent storage depots for water which the fish is unable to eliminate.

SUMMARY

Polycystic kidney is not uncommon in goldfish. The observation that it occurs in conjunction with neurofibromatosis, as well as among fish in isolated pools, suggests that it represents an inherited congenital abnormality.

Its pathogenesis is discussed with reference to renal morphogenesis as observed in the goldfish and with reference to the hypotheses advanced to account for polycystic kidney in man.

The fact that normally 85 per cent of nitrogenous waste is eliminated by the gills of these fish and that this proportion increases to 90 per cent in cases of polycystic kidney accounts for the absence of azotemia in the affected animals. Although edema and ascites are absent, the normal water balance is surely disturbed. The huge fluid-filled cysts that ultimately result may serve as storage depots for water that cannot be excreted.

All photographs were made by Mr. Joe Humphrey.

14. Copeland, D. E.: J. Morphol. **82**:201, 1948. Meyer.[7]

METABOLITE ANTAGONISTS IN EXPERIMENTAL CANCER

Guanazolo

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THE FIELD of metabolite antagonists is attracting considerable attention from the workers in the cancer field, and a number of antimetabolites are now being tested clinically as well as experimentally. While certain encouraging results have been reported by those using a folic acid antagonist in the treatment of leukemia (Reinhard, Good and Martin [1]), the toxic effect of this as well as of some other antimetabolites should not be minimized. Apparently the difference that exists between the inhibitory effect exerted by antimetabolites on cancerous tissue and the toxic effect on the host is small as long as both the cancer cells and the normal cells require the essential metabolite. Under these circumstances the announcement of Kidder, Dewey, Parks and Woodside [2] that they had found that cancer cells seem to be capable of metabolizing guanine, while normal mammalian cells cannot make use of dietary guanine and synthesize it from adenine, was received as a possible solution of this problem. Working on the animal micro-organism Tetrahymena geleii, they demonstrated that it was biochemically similar to the vertebrates in regard to amino acid and vitamin requirements.[3] They established, however, a difference between the protozoan and the vertebrate in the respect that there is a "total lack of sucrose-splitting enzymes, and presence of guanine and uracil requirements in *Tetrahymena*." It is known that while the Mammalia can synthesize

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1. Reinhard, E. H.; Good, J. T., and Martin, E.: J. A. M. A. **142**:383 (Feb. 11) 1950.

2. Kidder, G. W.; Dewey, V. C.; Parks, R. E., Jr., and Woodside, G. L.: Science **109**:511, 1949.

3. Kidder, G. W., and Dewey, V. C.: J. Biol. Chem. **179**:181, 1949.

guanine from adenine they cannot make use of dietary guanine for the reverse reaction.[4] Tetrahymena, on the other hand, cannot synthesize guanine but requires this purine in its diet.

Furthermore, Kidder and his co-workers found that the purine inhibitor known as guanazolo (5-amino-7-hydroxy-1H-v-triazolo [d] pyrimidine), an analogue of guanine, produced a strong inhibition of the growth of this protozoan. Having established these facts, Kidder and associates decided to determine whether or not cancer cells were similar to normal cells in this phase of purine metabolism. They chose a rapidly growing transplanted mouse adenocarcinoma, Eo771, and when the transplant was six days old they began daily injections of guanazolo, 0.5 mg. twice a day. According to them, "almost complete cessation of tumor growth resulted during guanazolo treatment . . ., but growth resumed shortly after the treatment was discontinued." Pathologic observations showed that the administration of guanazolo did not cause the death of the cancer cells but only checked their growth. Similar results were obtained with spontaneous mammary cancer of strain C3H [5a] mice. In this case the injection of guanazolo, 1.0 mg. twice daily, started when the tumor was about 0.2 cm. in diameter and a considerable, almost complete, retardation was observed. Kidder and associates concluded that "the data at hand . . . are consistent with the theory that the effect of guanazolo on cells of Eo771 is the same as in *Tetrahymena*." And although admitting that "it would be hazardous to assume that *all* malignant cells, unlike the normal, metabolize guanine and therefore will become inhibited by guanazolo," they expressed the hope that the result of their work offers "fantastic odds in favor of uniformity, at least in this respect, among the various cancerous tissues." [5b]

In our experiments we used August rat carcinoma, a fast growing tumor, which never regresses, at least in the strain we received from Dr. Francis Carter Wood. Altogether 280 rats of an average weight of 170 Gm. were used for this investigation.

In the first series of experiments 40 rats, of an average weight of 172 Gm., were submitted to treatment with guanazolo. The treatment was started when the transplant was six days old. It was of pinhead size and did not show any active growth in most of the animals.

The animals were given subcutaneous injections of guanazolo, twice a day, the total daily dose being 60 mg. per kilogram of weight, which corresponds to the dosage employed by Kidder and his co-workers in their experiments with mouse carcinoma Eo771. We obtained a con-

4. Brown, G. B.; Roll, P. M., and Plentl, A. A.: J. Biol. Chem. **172**:469, 1948.

5. Kidder and others: [2] (*a*) p. 513; (*b*) p. 514.

siderable but not complete inhibition in 30 rats (75 per cent), with a slow but steady growth in the rest of the tumors (25 per cent). At the end of three weeks of treatment the average size of the tumor was 2.2 cc., compared with 9.1 cc. in the control group of 20 rats (chart 1). The rat bearers of the tumors which continued to grow showed some sluggishness and loss of weight (12 per cent decrease in weight), while the ones with the growth inhibited or almost inhibited seemed to tolerate the treatment better and showed no substantial loss of weight (average gain of weight, 2.1 Gm.).

In the next series of experiments 40 rats with an average weight of 165 Gm. and with the transplants 12 days old were given a daily

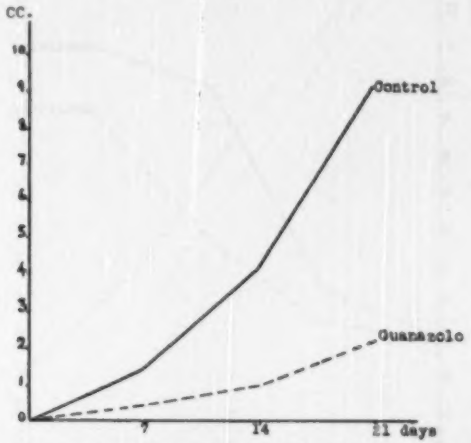

Chart 1.—August rat carcinoma. Forty rats were used in this experiment with guanazolo. Twenty rats served as a control. The average weight was 172 Gm. The dosage was 60 mg. per day per kilogram of weight. Subcutaneous injections started on the sixth day after transplantation, when the growth was of pinhead size.

total dose of 100 mg. per kilogram of weight of guanazolo. The average size of the tumor at the beginning of the treatment was 3.2 cc. In not a single case was a complete inhibition of the growth obtained, and at the end of fifteen days of treatment the average size of the tumor had increased to 5.6 cc., compared with 9.9 cc. in the control group of 20 rats, and to 9.2 cc. and 11.1 cc., respectively, at the end of three weeks (chart 2). This dose, however, produced a much stronger toxic effect on the cancerous rats, with 5 animals dead at the end of the experiment, while in the control group no mortality was observed, in spite of the large size of the tumors. The average loss of weight for

this group of treated animals was 18 per cent, or 30 Gm., while the average loss for the control group was only 11 Gm. Histologic examination of the adrenal glands of the treated animals revealed pathologic changes in the reticular and fasciculate zones. Degenerative changes were observed in the reticulum cells with pronounced vacuolation and disintegration of the argentaffin fibrils. No such lesions were observed in the adrenal glands of the control cancerous rats.

In the third series of experiments 40 rats with an average weight of 172 Gm. and with the transplants eleven days old were given a daily

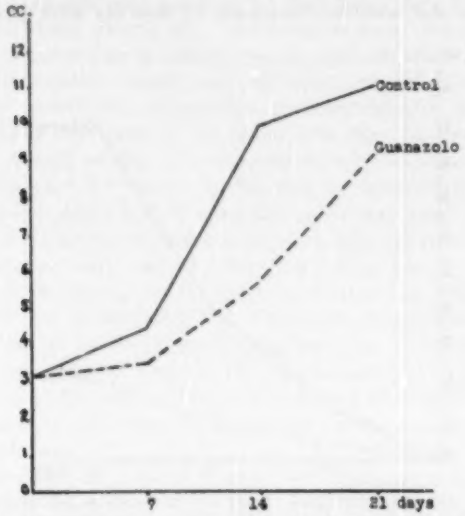

Chart 2.—August rat carcinoma. Forty rats were used in this experiment with guanazolo. Twenty rats served as a control. The average weight was 165 Gm. The dosage was 100 mg. per day per kilogram of weight. Subcutaneous injections started on the twelfth day after transplantation, when the growth was of an average size of 3.2 cc.

dose of guanazolo, 50 mg. per kilogram of weight. The initial size of the tumor was 3.4 cc. In this series no substantial retardation of the growth was noted. In the treated rats the tumor had increased on the average to 8.9 cc., compared with 10.3 cc. in the control group of 20 rats, at the end of fifteen days, and to 13.5 cc., compared with 14.0 cc., at the end of 21 days (chart 3). However, the toxic effect of the preparation was less apparent and the loss of weight in this group of rats was 8 per cent, or an average of 13.8 Gm.

In the next series of experiments 10 rats with large tumors, averaging 16.2 cc., were operated on and the tumors removed, with no apparent microscopic lesions being left. However, the presence of microscopic lesions was not excluded. All the rats recovered swiftly from the operation and from the second day were given guanazolo in a daily dose of 80 mg. per kilogram of weight for three weeks. In 2 rats no growth developed even after the treatment was stopped, which seems to indicate that the operation was complete. In the rest of the rats

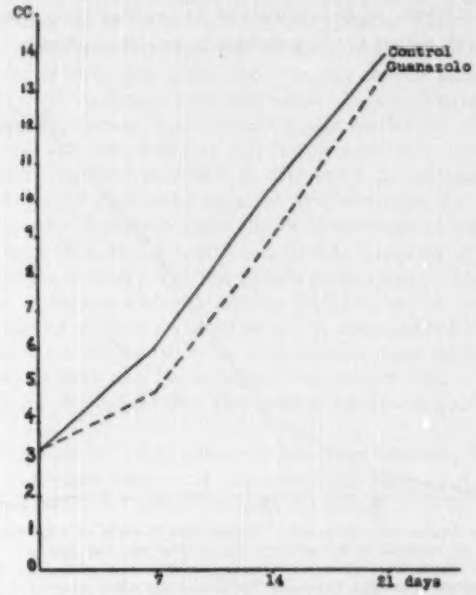

Chart 3.—August rat carcinoma. Forty rats were used in this experiment with guanazolo. Twenty rats served as a control. The average weight was 172 Gm. The dosage was 50 mg. per day per kilogram of weight. Subcutaneous injections started on the eleventh day after transplantation, when growth was of an average size of 3.4 cc.

the growth recurred in spite of the guanazolo administered to them. By the end of the third week the average size of the 8 tumors had reached 6.2 cc., which corresponded to the average size of the tumors of the control batch of 5 rats operated on, namely, 6.5 cc. By the end of the fourth week the average size reached 10.2 cc. and 9.9 cc., respectively (chart 4). Thus it seems that guanazolo has less or no inhibitory effect on the incipient form of growth when the transplant is well

adjusted to the host's body fluid, as is the case of a growth recurring after an operation.

The female rat bearers of August carcinoma when pregnant, as a rule, not only give birth to healthy progeny but take good care of them, even if the tumor is in an advanced stage. In 3 instances the rat bearers of August carcinoma were treated with guanazolo while pregnant, and in all 3 cases there was a miscarriage with all the progeny dead. Whether guanazolo interferes with normal pregnancy by exerting an inhibitory influence on the embryos or by exerting toxic effects on the cancerous rats we are not in a position to answer at present.

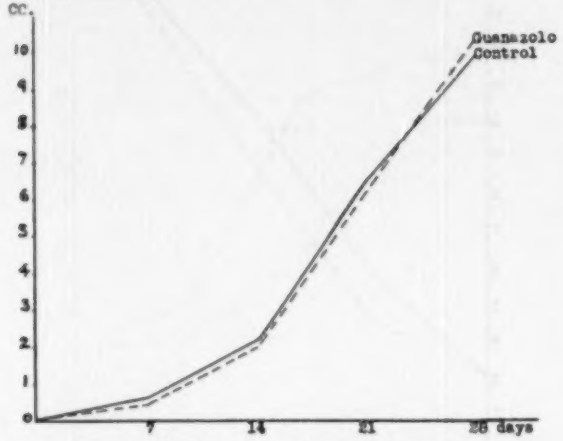

Chart 4.—August rat carcinoma. Thirteen rats, bearers of large tumors, were operated on for removal of the growths and divided into two groups. Five served as a control. Eight were given subcutaneous injections of guanazolo, 80 mg. per day per kilogram of weight, beginning the second day after removal of the tumor, when no palpable growth was present.

The observation that guanazolo in large doses apparently is more toxic to the rat bearers of advanced tumors than to those with incipient growths suggested that a test be made with this compound on normal rats. Twenty normal rats were given as large daily doses of guanazolo as 160 mg. per kilogram of weight for three weeks without any apparent ill effect. A higher dose, however, induced some sluggishness and loss of weight. Thus there seems to be some similarity between the action of guanazolo and that of bacterial polysaccharides, which are much more toxic to the rat bearers of tumors, even if the tumors are relatively small, than to normal rats. From the work of Diller, Blauch

and Beck [6] one might assume that the injury done to the adrenal gland, which is pronounced in cancerous mice treated with polysaccharides, might be the underlying factor in this phenomenon. Whether adrenal injury is the cause of the toxic effect of guanazolo when this is administered to cancerous rats is a subject for further investigation.

COMMENT

The assumption of Kidder and co-workers that cancerous cells differ from normal cells in their capacity to metabolize guanine apparently is not substantiated by the results of the investigation we have made with the antimetabolite guanazolo, at least as far as August rat carcinoma is concerned. If their assumption were true, the actively growing neoplastic tissue, with vigorous mitotic division of cells, would have required more guanine, an essential factor in nucleic acid synthesis.[7] The report of Kidder and associates concerns only incipient forms of growth, and no information has been published to date about the inhibitory effect of guanazolo on more advanced stages of adenocarcinoma Eo771 of the mouse. A six day transplant might still be in the stage of adjusting to the host's body fluid, and it is well known that a number of chemical substances might interfere with the growth at this stage. Unless it is proved that guanazolo exerts a definite inhibitory effect on a more advanced stage of cancerous growth or this is demonstrated by experiments in vitro, we feel that there is not a sufficient basis for the theory advocated by Kidder and his associates that cancer cells differ from normal cells in the respect that they cannot synthesize guanine from adenine.

The mechanism by which guanazolo exerts an inhibitory action on August rat carcinoma seems to be of a nonspecific nature, and its action might or might not be indirect through interfering with the growth-promoting factors of the organism.

SUMMARY

The effect of guanazolo (5-amino-7-hydroxy-1H-v-triazolo [d] pyrimidine), a guanine analogue, on transplanted August rat carcinoma was investigated.

Guanazolo produced some inhibitory effect on the growth when the transplant was six days or less old; however, it had no destructive action on this tumor. There was little or no effect if treatment was delayed until ten days after transplantation.

Guanazolo produced no inhibitory effect on the recurrence of the growth in rats whose tumors had been surgically removed.

6. Diller, I. C.; Blauch, B., and Beck, L. V.: Cancer Research **8**:591, 1948.
7. Hitchings, G. H.; Elion, G. B.; Vanderwerff, H., and Falco, E. A.: J. Biol. Chem. **174**:765, 1948.

Cancerous rats receiving 80 mg. of guanazolo per day per kilogram of weight for a period of two or three weeks manifested some toxic effect, which was apparent in loss of weight, sluggishness and pathologic changes in the adrenal glands. This toxic effect was much less pronounced in normal rats receiving guanazolo.[8]

8. Since this paper was submitted the following papers on guanazolo have appeared in the literature: Gellhorn, A.; Engelman, M.; Shapiro, D.; Graff, S., and Gillespie, H.: Cancer Research **10**:170, 1950. Sugiura, K.; Hitchings, G. H.; Cavalieri, L. F., and Stock, C. C.: ibid. **10**:178, 1950. A paper entitled "Nucleic Acids in Cancer" was read by Samuel Graff, at the Fifth International Cancer Congress in Paris, July 17, 1950.

STUDIES ON THE EFFECT OF RADIOACTIVE COLLOIDAL GOLD ON THE DEVELOPMENT OF THE ORAL STRUCTURES OF THE MOUSE

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CHICAGO

RECENT studies have shown that systemic administration of radioactive phosphorus will produce abnormalities in the development of the odontogenic tissues and adjacent structures.[1] Since systemic irradiation may produce these effects through changes in metabolism, it was felt that the problem could be elucidated by studying the effects of a locally injected colloidal suspension of radioactive gold.

Radioactive gold 198 is an emitter of beta rays with a small gamma component (approximately 15 per cent) as compared with radioactive phosphorus, which emits only beta rays. The isotope of gold which has a half-life of 2.7 days is made by exposing the stable isotope of gold to the neutron flux of the atomic pile. Colloidal suspensions may be obtained by a process which involves dissolving the gold in nitrohydrochloric acid and then adding ascorbic acid.[2]

METHOD

Approximately 0.025 cc. of colloidal gold 198 with an activity of 17 millicuries per cubic centimeter was injected adjacent to the left mandible in 26 immature mice (1 and 2 days of age). After injection, the animals were killed at intervals of 8, 13, 21, 28 and 60 days. The head was removed from each animal and fixed in 4 per cent formaldehyde. The head was split longitudinally so that each half could be sectioned separately. The tissues were then decalcified in formic acid, embedded in paraffin, sectioned serially and stained with hematoxylin and eosin, according to a modification of the method described by Morse.[3] Controls consisted of untreated animals and mice given an injection of nonradioactive colloidal gold.

From the Departments of Pathology, Washington University School of Dentistry and School of Medicine, St. Louis.

The radioactive material used in this investigation was supplied on allocation from the Isotopes Division, United States Atomic Energy Commission.

1. Burstone, M. S.: The Effect of Radioactive Phosphorus upon the Development of the Teeth and Mandibular Joint of the Mouse, J. Am. Dent. A., to be published.

2. Sheppard, C. W., and Hahn, P. F.: Techniques in the Handling of Radioactive Isotopes Used in Medical Therapy and the Preparation of Radioactive Colloidal Gold, Isotopes Division Circular 3, United States Atomic Energy Commission, November 1947.

3. Morse, Anna: J. Dent. Research **24**:143, 1945.

RESULTS

Gross Findings.—Radioactive Gold: Seven to 10 days after injection of the gold there was an impressive degree of epilation in the region of the injected area. This area became necrotic and after an interval of one or two weeks began to heal over, slowly forming a heavily keratinized scar. The animals exhibited facial hemiatrophy and notable occlusal imbalance involving the incisor teeth as an effect of radiation directed to one side of the developing mandible. In many of the mice the incisor tooth on the irradiated side was stunted and chalky white in appearance, while the incisor on the opposite side continued to grow because of a lack of attrition (fig. 1).

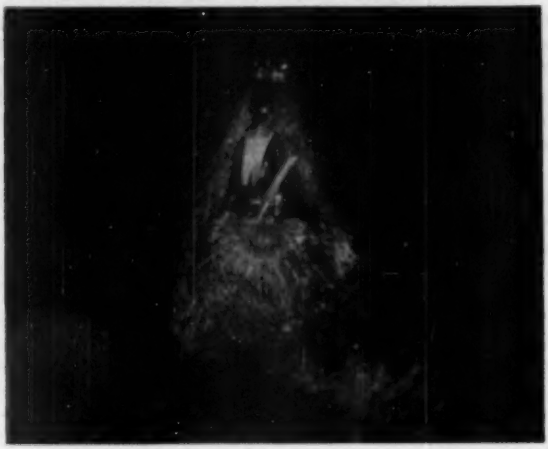

Fig. 1.—Occlusal imbalance and facial hemiatrophy as a result of injection of radioactive gold adjacent to the left side of the jaw. The lower left incisor is stunted.

Microscopic Observations.—Nonradioactive Colloidal Gold: In those animals receiving an injection of the colloidal gold control solution there were no histologic changes except for a mild inflammatory response and phagocytosis of gold particles in the adjacent soft tissue.

Radioactive Colloidal Gold: Eight days after the injection of the radioactive gold the pulps of the first and second molar teeth were aplastic, the second molar teeth showing the more pronounced change. The first molar exhibited osteodentine formation at the apical portion of the crown, while the second molar exhibited the same change and, in addition, irregular areas of predentine and a small amount of

osteodentine in the pulp. The odontoblastic layer in the apical area was irregular, and the odontoblasts lacked their normal columnar appearance. Likewise, in both first and second molars the ameloblasts toward the root portion of the crown appeared as low cuboidal cells. There

Fig. 2.—*A*, second (*a*) and first (*b*) molar teeth of animal 13 days after injection of radioactive gold; (*c*) osteodentine in pulp chamber; (*d*) aplastic marrow. *B*, second (*a*) and first (*b*) molar teeth of 14 day old normal control; note the greater extent of root formation, especially in the first molar; (*c*) ameloblastic layer; (*d*) enamel space; (*e*) dentine; (*f*) odontoblasts; (*g*) pulp.

was frank aplasia of the underlying alveolar bone with the presence of a network of spindle-shaped connective tissue cells, clumps of extra-

vasated erythrocytes and a scattering of macrophages. Osteoblastic activity was distinctly reduced. There was hyperkeratosis of the oral epithelium, and the rete was shallow. Many of the epithelial cells were enlarged and had hyperchromatic nuclei.

Thirteen days after the injection the coronal portion of the first molar tooth appeared well developed and had normal tubular dentine. Toward the apical portion, however, there had been a cessation of development, with formation of an irregular type of dentine similar to that described in the previous group. The pulp contained a scattering of pyknotic nuclei. Both odontoblasts and ameloblasts adjacent to the apical portion of the crown were irregular and flattened. There was a scattering of osteodentine throughout the pulp chamber of the second molar tooth, and the odontoblastic layer lacked continuity. The cells of the ameloblastic layer appeared as columnar cells only in an area adjacent to the coronal area of the second molar. The remaining cells of the ameloblastic layer were low cuboidal cells or else appeared as squamous type epithelium. There was no evidence of histogenesis of the third molar. Although the adjacent bone marrow was still aplastic, there appeared to be an increase in osteoblastic activity as compared with the previous postirradiation stage (fig. 2). The oral epithelium was still heavily keratinized, but the individual cytologic structure appeared normal. Some of the interdental papillae were necrotic. The adjacent mucous type salivary glands appeared relatively normal except for a moderate degree of acinous swelling and a slight distortion of the intra-acinous structure. Moreover, the nuclei were fewer than normal. The adjacent serous type glandular structure appeared condensed and contained pyknotic nuclei, and some acini contained empty cystlike areas. The ducts were unaltered. The teeth, the jaws and the salivary gland structure of the opposite side of the mouse, that is, the right side, exhibited little or no radiation changes as compared with the left side.

At 21 days the pulp of the first molar tooth was fibrotic. The reduced enamel organ appeared as squamous epithelium and contained areas of keratinization. Although apposition of the coronal dentine appeared to have occurred in a normal manner, formation of the root had been completely inhibited. The apical portion of the crown consisted of a mass of irregular dentine and osteodentine. The outline of the second molar tooth was more distorted, and the entire structure of the dentine was irregular and contained cell inclusions. A slight trace of enamel matrix was observed adjacent to the occlusal surface (fig. 3). The underlying alveolar bone disclosed irregular trabeculae with prominent cement lines but the osteoblastic activity was relatively normal. Bone marrow cellularity appeared normal except for fibrosis

in some areas. The oral epithelium was still heavily keratinized, and the interdental papillae were necrotic. There were foci of heterophilic granulocytes in the adjacent soft tissues. The salivary gland tissue was not appreciably changed as compared with that of the last series.

Fig. 3.—*A*, second molar tooth 21 days after radioactive gold had been injected into an adjacent area. There is a complete failure of root formation. (*a*) Oral epithelium; (*b*) enamel matrix; (*c*) dentine, exhibiting irregular tubular structure and trapped cell inclusions.

B, second molar tooth of a normal 22 day old control. Note the regular tubular structure of the dentine and the well developed tooth structure. (*a*) Dentine; (*b*) odontoblasts; (*c*) pulp.

On the twenty-eighth day the histologic picture was similar except for increased fibrosis of the pulp and diminished keratinization of the oral epithelium. The first and second molars were ankylosed to the underlying alveolar bone by what appeared to be secondary cementum

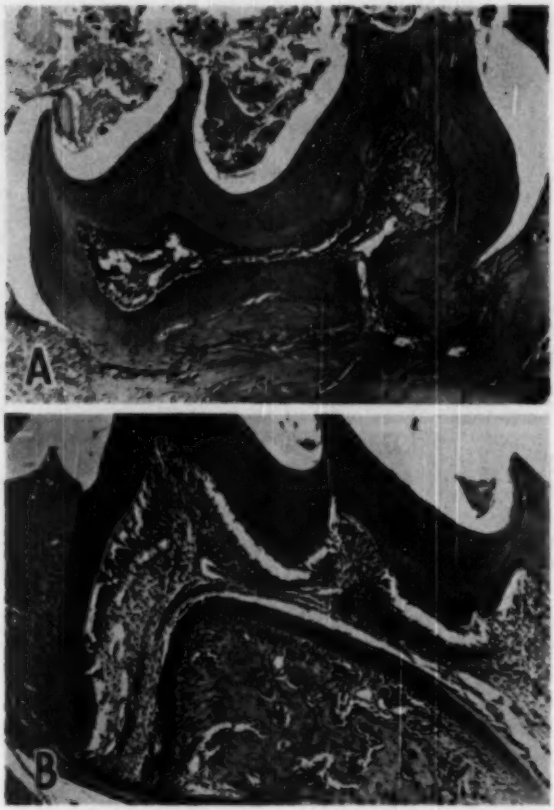

Fig. 4.—*A*, first molar tooth 28 days after irradiation. There is ankylosis of the crown and the underlying bone.

B, first molar tooth of normal 30 day old mouse, showing well developed root structure.

(fig. 4). In one of these animals a rudimentary third molar was present. Roentgenographic evidence confirmed these microscopic observations (fig. 5).

Two months after irradiation the changes were still similar to those of the last postirradiation stage. Failure of development of the root structure of the first and second molars and ankylosis of these teeth and the underlying alveolar bone were prominent. The inflammatory response of the adjacent soft tissues was still present, and some of the interdental papillae were necrotic. The structure of the mucous type glands was still distorted, and many of the nuclei were pyknotic. Areas of serous acini exhibited a moderate degree of fibrosis.

Fig. 5.—Roentgenogram of the left (*A*) and the right (*B*) sides of the head of the same mouse as in figure 4, showing absence of root formation as well as lack of third molar on the left (injected) side.

Observations on Side of Head Which Received Least Amount of Radiation.—In all the mice the side of the head opposite the area of injection presented slight changes as compared with the heavily irradiated side. Marrow aplasia and slight formation of osteodentine were present, but nevertheless, in all cases, the root structure developed normally. Macrophages containing a fine granular material, which was interpreted as representing particles of gold, were visible in the adjacent subcutaneous area, thus indicating some dispersal of the colloidal gold.

COMMENT

Since the beta component consists of a relatively soft type of radiation with a maximum energy of about 800 kilovolts, the greater part of the radiation damage will be confined to the first few millimeters of tissue adjacent to the injected colloidal suspension. Thus, the histologic changes represent a primary radiation effect, since the side of the head farther from the radiation source had a relatively normal development of tooth and bone structure. These findings are confirmed on a roentgenographic basis (fig. 5). The variation in degree of damage may be explained on the basis of uneven distribution of the suspension injected into the tissue.

The previous studies on immature mice which had received injections of soluble radioactive phosphorus solutions, a procedure resulting in irradiation of the whole body, revealed qualitatively similar development disturbances, closely paralleling those herein described.[1] This indicates that the changes in the teeth and the jaws caused by systemic uptake of radioactive materials represent primarily a direct radiation effect.

The relative radioresistance of mucous glands as compared with serous type glands has been observed in human material after local irradiation.[4]

CONCLUSIONS

The injection of colloidal radioactive gold adjacent to the jaw of the immature mouse will result in abnormalities of osteogenesis and odontogenesis, including failure of root formation.

The changes are interpreted as being the result of local irradiation, since the side of the head farther from the injected area exhibits relatively normal development of tooth and bone structure.

These changes are similar to those observed in immature mice receiving systemic dosages of radioactive phosphorus.

The serous type glands manifest a greater radiosensitivity than the mucous type. The duct elements are relatively radioresistant.

University of Illinois College of Dentistry.

4. Ackerman, L. V., and del Regato, J. A.: Cancer: Diagnosis, Treatment and Prognosis, St. Louis, C. V. Mosby Company, 1947, p. 105.

NONSPECIFIC PERIAPPENDICAL GRANULOMAS

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A NONSPECIFIC periappendical granuloma is a relatively rare lesion encountered by one interested in gastrointestinal surgery. The term is self explanatory in that it indicates the site of the lesion, plus the fact that it has no relation to the specific granulomas of tuberculosis, actinomycosis, amebiasis or lymphogranuloma. During the last nine months of 1948 one of us (J. E. M.) had the unusual experience of treating five of these lesions surgically. The 5 cases form the basis of this report. Those interested in the historical and statistical data relative to this condition should consult the article recently published by Wilson, Dockerty, Waugh and Bargen.[1]

REPORT OF CASES

CASE 1.—A 30 year old white woman had suffered from an acute attack of pain in the right lower quadrant of the abdomen one and a half years prior to her arrival at the Mayo Clinic. The pain had lasted two days and was associated with nausea and a low grade fever. She was up and around in a few days, but since this episode she had complained intermittently of pain in the right lower part of the abdomen. Six days prior to admission she again had pain and fever. At the time of examination, April 21, 1948, she had a low grade fever and was complaining of moderate pain in the right lower abdominal quadrant. There was a palpable, tender mass filling the lower portion of the right lower quadrant; on pelvic examination, this mass was thought to be rising from the right adnexal region. The laboratory reports were as follows: leukocytes, 13,000 per cubic millimeter of blood; hemoglobin, 11.6 Gm. per hundred cubic centimeters; urine, normal; erythrocyte sedimentation rate, 108 mm. in one hour (Westergren method). A diagnosis of torsion and subsequent infection of a right ovarian cyst was made, and the patient was operated on, April 22.

The abdomen was examined through a retracting incision made in the lower part of the right rectus muscle. The cecum was redundant and lay adjacent to the right adnexa, to which it was adherent. The appendix was involved in a thick, indurated, edematous mass lying in the ileocecal angle, the mass measuring about 10 by 4 by 3 cm. in size. An operative diagnosis of periappendical granuloma was

From the Division of Surgery (Dr. Musgrove) and the Division of Surgical Pathology (Dr. Dockerty), Mayo Clinic.

1. Wilson, J. W.; Dockerty, M. B.; Waugh, J. M., and Bargen, J. A.: Arch. Surg. **59**:933, 1949.

arrived at, but, owing to the fact that the granuloma was definitely fixed to the terminal part of the ileum and the posterior cecal wall, a right hemicolectomy was performed (fig. 1). The anastomosis was completed as a side to side ileotransverso-colostomy. Ten grams of sulfathiazole crystals were placed in the peritoneal cavity, and the abdomen was closed.

Postoperatively the patient was given penicillin and streptomycin intramuscularly and sulfasuxidine by mouth. She had an uncomplicated hospital convalescence, being dismissed on the tenth postoperative day. A follow-up letter on June 6, 1949 stated that she was having a slight increase in the number of stools but otherwise felt well.

Case 2.—A 78 year old white man was admitted to the hospital, May 11, 1948, with the tentative diagnosis of "partial intestinal obstruction, probably due to

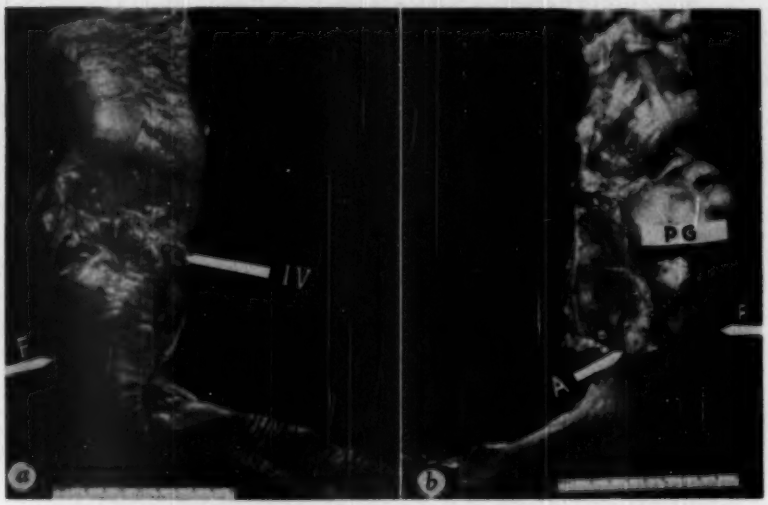

Fig. 1 (case 1).—(*a*) Anterior view of the periappendical granuloma, showing secondary involvement of the terminal part of the ileum with fistula formation (*F*), as seen from the mucosal surface. *IV* indicates the ileocecal valve. (*b*) Posterior view of the granulomatous mass. The appendix (*A*), which was buried, is shown in retrocecal position. *PG* indicates the periappendical granuloma; *F*, the fistula.

malignancy of the cecum." Eight days prior to admission he began to complain of moderately severe pain and tenderness in the right lower part of the abdomen and intermittent "gas pains." His bowels did not move for four days, and then, after use of a laxative, he passed copious watery dark stools for one day, with no exacerbation of his pain. His home physician had thought that the pain was due to his inguinal hernia on the right, for which he wore a truss. The pain in the right lower quadrant of the abdomen and the "gas pains" became progressively more severe until the time of his admission.

The history was somewhat inadequate, owing to language difficulty, but on careful inquiry the patient told of having had a severe attack of pain in the right lower

quadrant of the abdomen in 1944. This attack had "laid him up" for several days, and since that time he had had recurring bouts of right lower abdominal pain which had necessitated rest in bed for two or three days on several occasions.

On examination, the abdomen was moderately distended and diffusely tympanitic, and there was considerable tenderness and muscle guarding in the right lower quadrant. There was diffuse hyperperistalsis, most active in the region of the tenderness.

The patient was given penicillin and streptomycin intramuscularly. A Miller-Abbott tube was passed into the small bowel. The intestinal decompression quickly relieved him of distention and gas pains, but the right lower abdominal pain and tenderness persisted. When the tube was clamped, he again became distended and his pulse rate rose. With this poor response to conservative treatment, he was operated on, May 15, 1948.

The abdomen was examined through a retracting incision made in the midpart of the right rectus muscle. Lying in the right iliac fossa was a large, indurated mass which firmly fixed the cecum, the proximal part of the ascending colon and the terminal part of the ileum. The appendix could not be visualized. Through the anterior cecal wall, a rough, irregular lesion could be palpated, the lesion feeling not unlike a carcinomatous ulcer. With the latter diagnosis in mind, a right hemicolectomy was performed (fig. 2). While the granuloma was being freed by sharp and blunt dissection, a small abscess cavity was entered. The anastomosis was completed as an end to end ileotransversocolostomy by the three-bladed clamp technic. Ten grams of sulfathiazole, 1,000,000 units of penicillin and 1 Gm. of streptomycin were left in the peritoneal cavity, and the abdomen was closed, a drain being brought out through a stab wound in the flank.

Postoperatively the intramuscular injection of penicillin and streptomycin was continued, as was the intestinal decompression. The patient passed gas on the third day, and the tube was removed. There was little drainage through the stab wound, and the drain was removed on the sixth postoperative day. The patient made an uneventful recovery and was dismissed to his home 13 days after the operation. In a follow-up letter, June 21, 1949, the patient stated that he had been well but for an occasional abdominal pain following meals. His bowel habits had been normal.

Case 3.—This 62 year old white farmer entered the clinic Oct. 25, 1948, complaining of diarrhea of four months' duration, anorexia, loss of strength and loss of 15 pounds (6.8 Kg.). On examination an ill defined, slightly tender mass was found far laterally in the right side of the abdomen, extending from the level of the anterior-superior spine of the ileum to the right costal margin. The temperature was 103 F. The tentative diagnosis was a perforating carcinoma of the right side of the colon or an abscess of undetermined origin, and the patient was sent to the hospital for further investigation and treatment. For the next four days his temperature ranged between 100 and 104 F. On October 28 he was given sulfasuxidine by mouth and penicillin and streptomycin intramuscularly, and in two days his temperature was normal. The laboratory reports were as follows, October 26: leukocyte count, 12,600 per cubic millimeter of blood; hemoglobin content, 14 Gm. per hundred cubic centimeters; erythrocyte count, 4,680,000; erythrocyte sedimentation rate, 81 mm. in one hour; urine, normal; stool, absence of blood. Roentgenograms of the thorax and plain roentgenograms of the abdomen did not disclose any abnormality. On October 29 the leukocyte count was 7,800 but the erythrocyte sedimentation rate had increased to 94 mm. Sigmoidoscopic examination gave normal results. On November 1 studies with the aid of a barium sulfate enema likewise gave negative results.

With subsidence of fever the abdominal mass became more definite and seemed to involve the region of the ascending colon. An excretory urogram, November 3, showed a normal condition. The negative results on examination with the aid of a barium sulfate enema, the absence of blood in the stool, the normal value for hemoglobin and the normal erythrocyte count certainly militated against the diagnosis of carcinoma of the colon, but, on the other hand, the history and the physical findings made it impossible to rule out this lesion. In a man of his age, surgical treatment was therefore to be advised, the preoperative diagnosis being periappendical granuloma versus carcinoma of the cecum or the ascending colon.

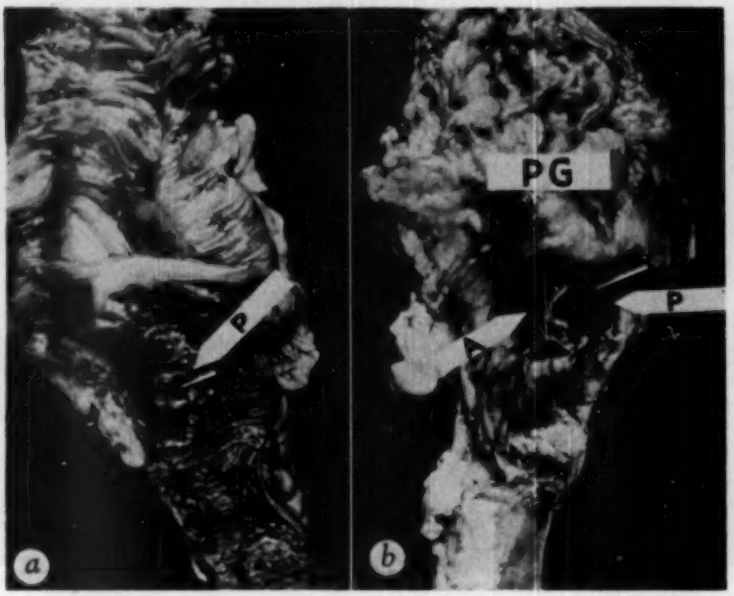

Fig. 2 (case 2).—(*a*) Anterior view: The boggy appearance of the ileal and cecal mucosa over the bulging granulomatous ileocecal mass is apparent. Secondary perforation of an abscess, extending into the cecum, is indicated by the arrow (*P*). (*b*) Posterior view: Dissection on the serosal surface reveals the perforated appendix (*A* and *P*) in retrocecal position, lying in the wall of a chronic abscess. *PG* indicates the periappendical granuloma.

A primary right rectus incision was made. The proximal portion of the ascending colon was fixed to the right colic gutter by a large, indurated, nodular mass. The first impression was that we were dealing with a carcinoma of the colon, but on further exploration the proximal half of the appendix was found lying free in the retrocecal fossa, the distal half being incorporated in the indurated mass. This finding was certainly in favor of a periappendical granuloma, but carcinoma still could not be entirely excluded. There was no evidence of metastasis. A right hemicolectomy was carried out after this lesion had been freed from the colic gutter

by sharp and blunt dissection (fig. 3). An end to end ileotransversocolostomy was performed by using the three-bladed clamp. Five grams of sulfathiazole crystals were left in the peritoneal cavity, and the abdomen was closed.

The postoperative regimen consisted of gastric suction until gas was passed by rectum on the third day, and the administration of penicillin and streptomycin was continued for one week. The patient was dismissed from the hospital on the tenth postoperative day, having had an uneventful convalescence. In a follow-up letter, June 13, 1949, he stated that he was in excellent health, his only complaint being slight diarrhea if he drank too much beer.

CASE 4.—A 56 year old white man was quite well until injured on Oct. 10, 1948. He was driving a logging tractor, which tipped, throwing him clear, and he landed on his right side across a log. He was able to get up immediately and walked some

Fig. 3 (case 3).—(*a*) Anterior view: The mucosa (*M*) overlying the granuloma is edematous but intact. (*b*) Posterior view: The diseased appendix (*A*) is visulized on the outer surface of the granuloma (*G*).

distance before he began to notice a pain in his right hip. This pain persisted, keeping him awake that night and making him walk with a limp. He was unable to return to work, the pain gradually extending down the medial side of his thigh to the knee. He had slight anorexia but no nausea, and his bowels continued to move normally. A few days later he began to notice night sweats. He was admitted to a hospital in Rochester on November 2, by which time he had lost 20 pounds (9.1 Kg.). He complained of pain in his right hip and right knee along with pain situated in the right lower part of the abdomen. His temperature was 101 F. On examination there was a suggestion of fulness in his right flank anteriorly, this area being quite tender to palpation, and even though there was considerable voluntary muscle guarding, a mass could be felt. There was great tenderness in the right costovertebral

angle. The intestinal sounds were normal. His right hip was normal to inspection and palpation, but extension of the joint caused pain in the hip and right lower part of the abdomen. Rectal examination gave negative results. On completion of the physical examination the suggested diagnoses were retroperitoneal hematoma, perinephritic hematoma and possible fracture in the region of the right hip.

The patient was given a light diet, and 300,000 units of penicillin G was administered daily. His subsequent hospital course was very interesting. His temperature ran a septic, swinging course. On November 11 he was given streptomycin intramuscularly, plus the penicillin, and five days later his temperature became normal. During this time he continued to complain of anorexia and pain in the right hip. On November 12 he was found to have wasting of the right thigh, spasm of the adductor muscles and a 20 degree flexion deformity of the right hip. This flexion deformity increased over the next 10 days to approximately 30 degrees.

The results of laboratory studies during this interval were as follows: On November 3 the value for hemoglobin was 12.1 Gm. per hundred cubic centimeters of blood, the erythrocytes numbered 4,070,000 and the leukocytes 17,400, the sedimentation rate was 115 mm. and roentgenograms of the pelvis, the right hip, the spinal column and the thorax disclosed no abnormality except slight hypertrophic changes in the lumbar part of the spinal column and a soft tissue mass in the right lower abdominal quadrant. On November 4 the excretory urogram did not disclose any abnormality and the soft tissue mass described in a foregoing paragraph was still present. On November 10 the leukocyte count was 19,400 and the sedimentation rate was 115 mm. On November 16 a barium sulfate enema study of the colon and terminal part of the ileum gave normal results.

At the completion of the investigation we were still thinking in terms of an infected retroperitoneal hematoma, but we also began to suspect the presence of a periappendical granuloma. Whatever the process was, we knew it was involving the iliopsoas muscle, with an increasing flexion deformity of the hip. It was on this account that we decided to operate. Preparation of the colon was started on November 18, the patient being given sulfasuxidine, and the operation was carried out on November 22.

The abdomen was examined through a retracting incision in the midpart of the right rectus muscle. The appendix was retrocecal, its tip entering a firm, knobby mass lying posterior to the cecum and ascending colon. There was no line of cleavage between the mass and the bowel; thus it was necessary to do a right hemicolectomy (fig. 4). The granulomatous mass had burrowed deeply into the iliopsoas muscle and had to be dug out by combined sharp and blunt dissection. An end to end anastomosis of the ileum and the transverse colon was carried out over a three-bladed clamp. Five grams of sulfathiazole, 1,000,000 units of penicillin and 1 Gm. of streptomycin were left in the peritoneal cavity, and the abdomen was closed without drainage.

The postoperative regimen was the same as that used in cases 1, 2 and 3. The patient passed gas on the third day, and the gastric suction tube was removed. On the seventh day there developed acute distention of the small bowel, which responded readily to the use of a Levin suction tube. The most interesting aspect of the postoperative course was the fact that as soon as the patient regained consciousness he was able to extend his right hip without pain. He was walking normally and feeling much improved when dismissed from the hospital on the twelfth day. In a letter received from him, June 16, 1949, he stated that he had quickly regained his health, having no further trouble with his hip or bowels.

CASE 5.—A 52 year old farmer with a main complaint of pain in the right lower quadrant of the abdomen was admitted to the hospital on Nov. 26, 1948. For one and a half years prior to admission he had noticed increasing fatigue and weakness. For the past year he had noticed that his stools were smaller than normal, being the "size of a small finger," but he had not noticed blood or mucus. He was aware of a mass and slight discomfort in the lower right part of the abdomen for five months, and during this time he lost several pounds in weight. Ten days prior to being admitted to the hospital he had moderately severe generalized abdominal pain, which kept him awake all night, and the following day the pain localized in

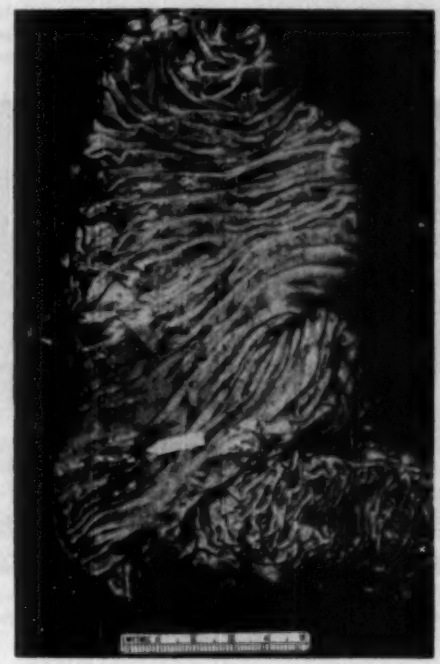

Fig. 4 (case 4).—Periappendical granuloma showing an impending perforation directed toward the cecum (arrow).

the right lower quadrant. This pain persisted, and he felt "slightly feverish." His bowels moved daily, the stool being yellow and watery.

His temperature on admission was 101 F. There was a visible fulness in the lower right quadrant of the abdomen, with moderate tenderness and voluntary muscle guarding in this region, making it difficult to outline the mass accurately, but the mass gave the impression of being the size of a large orange and fixed deep to McBurney's point. This region was dull to percussion, while the intestinal sounds were normal or slightly hyperactive. Rectal examination gave normal results.

The history and the physical findings certainly suggested a perforating cancer of the cecum or the proximal part of the ascending colon, but periappendical granuloma could not be ruled out. The patient was given moderate doses of penicillin and streptomycin, and in three days his temperature became normal and he was feeling much better.

The results of laboratory investigation were as follows: On November 26 the erythrocytes numbered 3,860,000 per cubic millimeter of blood, the hemoglobin content was 12 Gm. per hundred cubic centimeters, the leukocyte count was 17,200, the urinalysis showed 20 pus cells per high power field and albuminuria (grade 3 on a basis of 1 to 4), and roentgenograms of the thorax and plain roentgenograms of the abdomen did not disclose any abnormality. On November 27 the erythrocyte sedimentation rate was 64 mm., and the blood smear was not diagnostic. On November 29 the excretory urogram was noncontributory. On November 30 the

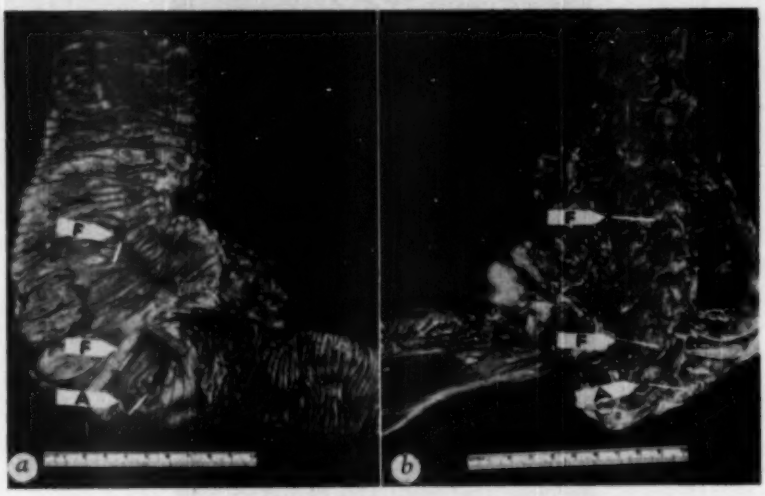

Fig. 5 (case 5).—(*a*) Anterior view: On the mucosal surface, fistulas (*F*) leading into the cecum and the ascending colon are apparent. (*b*) Posterior view: The diseased appendix (*A*) is buried in the granulomatous retrocecal mass. There are also cut sections of several fistulous tracts.

roentgenologist, when he examined the colon, said that "the terminal ileum and appendix were not seen at this examination. The cecum appeared to be fixed, possibly due to an extrinsic process."

The patient was given a nonresidue diet and sulfasuxidine orally for four days prior to operation on December 3. The preoperative differential diagnosis was perforating cancer of the right portion of the colon versus periappendical granuloma. With the latter diagnosis in mind, a small muscle-splitting incision was made in the right lower quadrant, the purpose being an operative procedure limited to exploration if cancer could be ruled out.

A large, indurated, knobby mass was found lying behind the upper portion of the cecum and the ascending colon. No portion of the appendix could be found;

thus a periappendical granuloma was strongly suggested. However, after considerable deliberation, cancer could not be ruled out on the basis of either the history or the operative findings; therefore a right hemicolectomy was performed. The wound was enlarged to the costal margin above and to within 1½ inches (38 mm.) of the pubic tubercle below, by splitting the external oblique and cutting the internal oblique and transversus muscles. With this excellent exposure, the right portion of the colon and the terminal part of the ileum were freed by blunt and sharp dissection (fig. 5), and an end to end ileotransversocolostomy was carried out with the use of a single Furniss clamp. Five grams of sulfathiazole crystals, 1,000,000 units of penicillin and 1 Gm. of streptomycin were left in the peritoneal cavity, and the abdomen was closed without drainage.

The postoperative regimen was the same as that in case 4. The patient began to pass gas on the third day and was getting along quite well. However, on the fourth day he complained of pain and tenderness in both calves; so dicumarol* therapy was instituted. Other than this setback, which cleared up in a few days, he had an excellent recovery. He reported to the clinic on June 12, 1949, at which time he stated that instead of having his usual two bowel movements a day, he had continued to have three movements daily, usually one after each meal. His wound was well healed, with no evidence of muscular weakness.

PATHOLOGIC ASPECTS

Grossly, the most outstanding feature in the five cases reported herein was the presence of retrocecal (three cases) and ileocecal (two cases) granulomatous masses measuring 6 to 12 cm. in diameter. In cases 1 and 4 the diseased appendix was buried in masses which were adherent to the terminal part of the ileum and the ascending colon (fig. 1). In the remaining cases portions of the appendix were visible prior to separation of adhesions (fig. 3).

The mucosa of the large and small intestines was edematous in those areas which overlay the granulomatous masses. In case 1 a granulomatous abscess had perforated into the terminal part of the ileum, and in cases 2, 4 and 5 fistulas leading into the cecum were present. In case 5 there was, in addition, a second fistulous tract which led into the ascending colon (figs. 1 to 5).

In all five cases there were areas in which the lumen of the bowel was compromised by the encroachment of the periappendical tumefaction.

When the appendixes were dissected out, it appeared that they were all enlarged and boggy because of edema. In case 1 there was evidence of rupture in the midportion along the line of the mesoappendical attachment. In cases 3 and 5 rupture had apparently occurred at the tip. All the appendixes were retrocecal or ileocecal in position, but in none of them were we able to demonstrate the original obstructing mechanism which had led to perforation.

On section of the periappendical masses in case 5 a subacute abscess 8 cm. in diameter was exhibited, while in the other cases multiple small abscess pockets were featured. The tissues were in general edematous and soft, but in every instance there were areas of reactive or "ligneous perityphlitis."

Microscopically, the tumors exhibited varying degrees of acute, subacute and chronic inflammation, predominantly proliferative in character in every instance. Fibrous connective tissue made up the bulk of the masses, and this varied in consistency from loose edematous fibroblastic proliferations containing a rich capillary network of blood vessels to dense hyaline scar tissue. Scattered throughout the granulomas were abscesses which varied greatly in size and in acuteness or chronicity. In case 1 there were large coalescing pus pockets filled with segmented granulocytes and scattered masses of fibrin. In some of the other cases there were similar but smaller foci of an acute on a subacute exudative process. Most of the abscesses, however, were of a more chronic nature, with plasma cells, lymphocytes and eosinophilic granulocytes in abundance. Foam cells were numerous, and foreign body giant cells, found in all five cases, were taken as indication of spilling of bowel contents, either from the ruptured appendix or from secondary fistulas. Such appendical defects resulting from rupture were found in three cases, and in one additional case there were areas of ulceration of the appendical mucosa. Edema of the tissues was a distinct feature in most cases, increasing the bulk of the granuloma, but thrombosis of blood vessels was not observed in the sections. In several instances edema of the walls of arteries and veins was prominent. Regional nodes were large and edematous.

Needless to say, careful search failed to reveal evidence of tuberculosis, actinomycosis, amebiasis and other lesions such as regional enterocolitis which can at times produce ileocecal granulomas.

ETIOLOGIC FACTORS

Perforative disease of the appendix appears to have been the etiologic basis for the nonspecific periappendical granuloma in the five cases which we have described, and this has also been true in similar cases encountered at the clinic. One naturally asks, then, the question "Why did not the course in these cases follow that of acute appendicitis?" Two factors deserve consideration in this regard, namely, the age of the patients and the position of the appendix.

In this as in other comparable series the position of the appendix has been either retrocecal or curled up in the ileocecal angle. In these positions there is better opportunity for sealing off the primary inflammatory focus. The parietal peritoneum is thus protected, and typical symptoms do not ensue. Adhesions form, and it is often not until a mass forms that the patient is aware of the existence of serious intra-abdominal disease.

Age is probably related to the rapidity of progression of the inflammatory process. It will be noted that only one of our patients was less than 50 years of age. Dennis [2] showed that the appendix is an organ

2. Dennis, C.: Arch. Surg. **43**:1021, 1941.

of active secretion. Bohrod [3] has pointed out that the lymphoid component of the appendix reaches a maximal degree of development about the tenth year and then gradually diminishes in amount. At all ages, but especially during the second decade of life, when the muscular coats of the appendix attain full development, this lymphoid tissue may respond to infections and other stimuli with consequent obstruction of the appendical lumen. With appendicular obstruction operating at all ages as the prime cause of appendicitis, it can readily be understood how distention of such an appendix will vary in degree and rapidity of development according to age. In the young patient gangrene theoretically should ensue early, before the defense processes can localize the infection. In the old there is more time for mobilization of defenses to accomplish the sealing-off process. This concept provides a logical explanation for the infrequency of periappendical granulomas in young patients, since a retrocecal position of the organ is not limited to the older age groups.

The fibroblastic reaction is the remaining feature which, in its walling-off capacity, provides the tumefactive characteristics of the condition and which brings carcinoma of the cecum into the differential diagnosis. While sealing off and at times actually burying the appendix, it protects the general peritoneal cavity from contamination. At the same time it renders difficult or impossible the operation of appendectomy even when to the surgeon it appears that the appendix has been the prime cause of the trouble.

SURGICAL ASPECTS

A right hemicolectomy is certainly a radical procedure for the removal of a benign lesion caused by inflammation of the appendix. However, an operation of this magnitude is usually necessary in dealing with a nonspecific periappendical granuloma for two reasons, the first being the fact that the surgeon can rarely exclude an underlying cancerous lesion at the time of exploration and the second being the inability to find cleavage planes between the granuloma and the bowel. In the past, in many cases the lesion must have been considered inoperable carcinoma and a palliative ileocolostomy carried out to divert the fecal stream. This operation often aided in the recovery, and much to the surgeon's surprise the patient remained well. This situation might well be compared to chronic pancreatitis for which the surgeon has done a cholecystoenterostomy thinking the lesion cancerous and telling the relatives that the prognosis was a matter of the patient's living for only a few months.

At the present time a periappendical granuloma might be treated by one of five different methods: (1) conservative treatment with low residue diet, diathermy, sulfonamides and antibiotics; (2) exploratory

3. Bohrod, M. G.: Am. J. Clin. Path. **16**:752, 1946.

laparotomy plus the medical measures just now mentioned; (3) removal of the appendix and the surrounding granuloma; (4) ileocolostomy with or without exclusion of the right portion of the colon, and (5) right hemicolectomy with extirpation of the lesion. These varying methods of treatment will now be discussed in more detail.

The conservative treatment presupposes an accurate diagnosis of periappendical granuloma and exclusion of cancer. In three of the five cases we have reported the history was strongly suggestive of cancer, and this is true for the majority of cases of this lesion. The laboratory investigation should include the following: erythrocyte count, hemoglobin concentration, leukocyte count, erythrocyte sedimentation rate, excretory urogram if the mass is in the region of the kidney, urinalysis, examination of the stool for blood and roentgenologic studies with the aid of a barium sulfate enema. A secondary anemia points toward a cancer, and the presence of blood in the stool is strong support for this diagnosis. Leukocytosis and a rapid sedimentation rate will indicate the presence of infection but will be of little help in the differential diagnosis. The urinalysis and the urogram will rule out renal lesions. Roentgenograms of the colon made with the aid of the barium sulfate enema should be of considerable help in differential diagnosis. In two of the five cases (1 and 2) in our series no barium sulfate enema roentgenograms were made, for the colonic lesion was not suspected in the first case, and there was obstruction in the second. However, in the last three cases (3, 4 and 5) roentgenograms of the colon were obtained; these did not show any abnormality in the third and fourth cases, while in the fifth case the cecum was "fixed, possibly due to an extrinsic process." We know that the cecum and proximal part of the ascending colon were also fixed in the third and fourth cases, but this finding was not reported by the roentgenologist. This fixation of the cecum and ascending colon plus the lack of mucosal deformity will favor an inflammatory lesion, for a cancer of the proximal part of the right side of the colon large enough to be palpated will almost invariably have produced a definite mucosal defect. However, even with this thorough investigation, cancer can rarely be excluded, the patient usually coming to operation.

Exploratory laparotomy is the next step on the diagnostic ladder, but in a good number of cases it is not the final step. In two of the five cases no portion of the appendix could be found on exploration. Therefore, were the large, knobby, indurated masses periappendical granulomas or were they cancers? We feel that the pathologist should answer this question after the mass is removed. When the appendix is found leading into the mass, the surgeon can make the diagnosis with a high degree of accuracy, but he still cannot definitely exclude the possibility of a neoplasm. Therefore, if the patient's condition will permit, we recommend an extirpative operation, rather than conservative therapy, under these conditions.

The ideal operation is removal of the appendix and the surrounding granuloma. Unfortunately, this operation is seldom feasible, owing to the lack of cleavage planes between the granuloma and the surrounding bowel wall. Not only were there no cleavage planes in the five cases we are reporting but, in addition, there were perforations extending from the granuloma into the lumen of the bowel in three cases, and perforation impended in a fourth.

The fourth method of dealing with this lesion is the sidetracking operation of making an anastomosis between the ileum and the transverse colon. This procedure will prevent obstruction and aid in the resolution of the granuloma, particularly if an exclusion type of operation is performed. Again, however, the surgeon is left with a question in mind: "Is there an underlying cancer?" Prior to the days of chemotherapy and antibiotics, the sidetracking ileotransversocolostomy was the best method of handling this lesion, this being the first stage of a two stage right hemicolectomy. However, with the advances in colonic surgery during the past decade, it is now seldom necessary to do a two stage removal of the right portion of the colon.

The final method of treating a periappendical granuloma is the one stage right hemicolectomy. This is the operation performed in all five of our cases and is the operation best suited for removal of most of these lesions. Technically, dissecting the granuloma free is the one difficult step in this procedure. The peritoneum should be incised lateral to the cecum and ascending colon, and the granuloma freed mainly by blunt dissection. If the lesion is lying high, one needs to be careful of the retroperitoneal duodenum, and if the lesion is low, the ureter may be difficult to distinguish. If the patient has had preoperative preparation of the colon, the surgeon may do an open or a closed anastomosis, depending on his preference. However, if the colon has not been prepared, we prefer a closed end to end anastomosis, as utilized in the last four cases.

SUMMARY AND CONCLUSIONS

We present in detail five cases of nonspecific periappendical granuloma in which operation was performed during the last nine months of 1948. One stage right hemicolectomy was performed in all five cases, with excellent results. The pathologic and surgical aspects of this rather uncommon lesion are discussed at some length. It is difficult, if not impossible, in the majority of cases of nonspecific periappendical granuloma to exclude definitely an underlying cancer. The ideal operation is appendectomy with removal of the surrounding granuloma, but this is an ideal seldom accomplished, owing to intimate connections of the granuloma and the adjacent bowel wall. The operation we recommend is the one stage right hemicolectomy.

PATHOLOGY OF EARLY AMEBIC HEPATITIS

An Experimental Study

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AMEBIC hepatitis is a form of early regional hepatic necrosis associated with massive invasion of the affected area by Endamoeba histolytica. It differs from amebic abscess [1] of the liver in that the process has not yet progressed to the stage of advanced colliquative necrosis with walling off from the surrounding hepatic parenchyma. Even before the discovery of E. histolytica by Lösch in 1875, Ballingall [2] suspected that there was an etiologic relationship between certain types of tropical dysentery and hepatic disease. In 1891 Councilman and Lafleur,[3] in a detailed clinical and pathologic study of amebiasis, first pointed out the various stages of hepatic involvement in amebic infection. In this excellent contribution, not only did they describe in detail the gross and the histologic picture of the classic, well developed amebic abscess of the liver, but in their investigation of several patients who died with early hepatic lesions they were able to establish criteria which are still valid in the interpretation of the pathogenesis of hepatic amebiasis in any of its forms.

Most of the literature on amebiasis of the liver is concerned with amebic abscess, and there are few reports dealing with early amebic hepatitis.[4] Rogers [5] was the first to emphasize the clinical as well as the pathologic distinctions between amebic hepatitis and "amebic liver abscess," and suggested rational forms of treatment based on the patho-

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1. Common usage justifies the term "amebic abscess of the liver" in spite of the well known fact that the lesion so designated is not a true abscess.

2. Ballingall, G.: Practical Observations on Fever Dysentery, and Liver Complaints as They Occur Amongst the European Troops in India, Edinburgh, D. Brown & A. Constable, 1818; cited by Councilman and Lafleur.[3]

3. Councilman, W. T., and Lafleur, H. A.: Johns Hopkins Hosp. Rep. **2**:395, 1891.

4. Ochsner, A., and DeBakey, M.: Surgery **13**:460 and 612, 1943; Surg., Gynec. & Obst. **69**:392, 1939. Ochsner, A.; DeBakey, M., and Murray, S.: J. Internat. de Chir. **4**:509, 1939.

5. Rogers, L.: (*a*) Lancet **1**:463, (*b*) 596 and (*c*) 677, 1922.

genesis and pathology of the lesions. Although aware of the various routes by which amebas might enter the liver as originally postulated by Councilman and Lafleur, Rogers favored the portal vein as the most probable, an opinion which has received strong support from a critical analysis of human material [6] and from experimental studies in various species of animals.[7]

Meleney [8] stated that amebic hepatitis is "well recognized" clinically and that pathologically it probably represents the first stage of abscess formation. Sodeman and Lewis [9] recently summarized the clinical findings in amebic infections of the liver and emphasized the importance of early clinical diagnosis. They expressed the opinion that a definite diagnosis of amebic hepatitis without abscess cannot be established by any means short of autopsy. As an indication that clinicians are generally unaware of amebic hepatitis, it may be pointed out that Simonds [10] failed to mention it in his review of the complications of amebiasis in fatal and nonfatal cases. Faust [11] expressed the belief that amebic invasion of the liver is probably much more common than the records indicate.

While experimental study of amebic colitis is comparatively easy, scant success has attended investigations of amebic hepatitis. Dale and Dobell [12] produced amebic colitis in 120 cats but did not observe hepatic involvement in a single one of their animals. While working with dogs, Faust [13] reported hepatic amebiasis observed in 1 of 100 animals with experimentally induced colonic infection. Moreover, 28,000 to 3,000,000 cultured trophozoites of E. histolytica of human origin injected into the portal vein of each of 12 kittens failed to produce amebic lesions in the liver.[14]

Because of the scarcity of pathologic studies of the early lesions of experimental amebic hepatitis, the following report seems justified.

MATERIAL AND METHODS

In the course of an experiment on amebic colitis in which 183 kittens were inoculated per rectum with E. histolytica of human origin, hepatic lesions developed in 2 of the animals. The 2 kittens died fourteen and seventeen days, respectively, after rectal inoculation and seven days after the establishment of acute amebic dysentery. Autopsies were performed while the bodies were still warm. The livers of these 2 kittens constitute the object of the present study.

6. Palmer, R. B.: Arch. Path. **25**:327, 1938.
7. Ratcliffe, H. R., and Geiman, Q. M.: Arch. Path. **25**:160, 1938. Frye, W. W.; Gabaldon, A., and Meleney, H. E.: J. Parasitol. **23**:229, 1937.
8. Meleny, H. E.: J. A. M. A. **103**:1213, 1934.
9. Sodeman, W., and Lewis, B. O.: J. A. M. A. **129**:99, 1945.
10. Simonds, J. P.: Quart. Bull., Northwestern Univ. M. School **17**:25, 1943.
11. Faust, E. C.: Tr. & Stud., Coll. Physicians, Philadelphia **11**: 101, 1943.
12. Dale, H. H., and Dobell, C.: J. Pharmacol. & Exper. Therap. **10**:399, 1917.
13. Faust, E. C.: Am. J. Trop. Med. **14**:221, 1934.
14. Carrera, G. M.: Unpublished data.

Bits of unfixed hepatic tissue from the affected areas were compressed under a cover slip on a glass slide and examined microscopically. Other portions of liver tissue, including the lesions, were fixed in Zenker's fluid and in 4 per cent formaldehyde solution for histologic study. Serial sections were made when indicated. Special staining for glycogen, reticulum, calcium, bacteria and connective tissue was done on representative sections. Iron-hematoxylin stains to bring out nuclear detail in E. histolytica were also made. The great majority of the sections were stained with hematoxylin and eosin, which proved to be satisfactory for general histologic detail as well as for amebas.

OBSERVATIONS

Gross Findings.—The livers were of normal size and shape. One had a single lesion, while the other had seven similar lesions distributed in various lobes. The lesions resembled one another except for variations

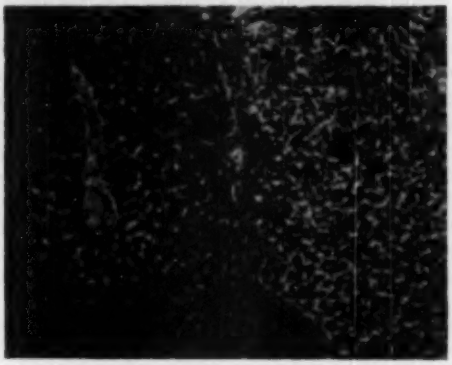

Fig. 1.—The lesion of early amebic hepatitis (on the right) is sharply demarcated from the normal adjacent liver tissue. Hematoxylin and eosin; × 120.

in greatest diameter, ranging from 0.5 to 1.5 cm. They were subcapsular in location and roughly wedge shaped. The lesions were yellowish pink, finely granular and softer than the adjacent normal hepatic tissues, from which they were sharply demarcated. No liquefaction was evident.

Direct Microscopic Examination Before Fixation.—Motile E. histolytica trophozoites were observed in the crushed preparations of the liver lesions in each instance.

Histologic Observations.—The most striking change was necrosis of most of the hepatic cells in the involved areas. At the margins of each lesion there was an abrupt transition to hepatic tissue of normal appearance (fig. 1). On close examination amebas were found only occasionally in the lumens of the large branches of the portal vein (fig. 2*A*), but numerous amebas were present in some of the smaller ramifications of

these veins and in the adjacent sinusoids of the hepatic lobules (fig. 2 *B*). In both the large and the small portal vessels where amebas were present, there was evidence of early thrombus formation. There was also a mild degree of local inflammation of the blood vessel wall. The hepatic cells in the periportal areas around these veins showed a variable degree

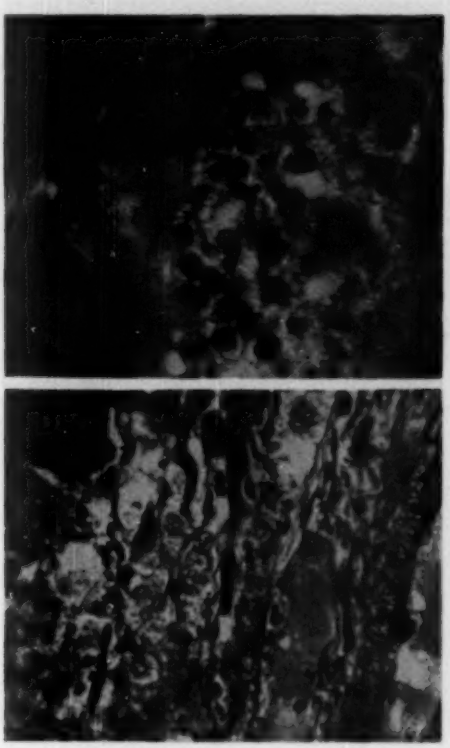

Fig. 2.—*A*, high power view of the lumen of a large branch of the portal vein showing a focus of fibrin, leukocytes and one ameba (indicated by arrow). Hematoxylin and eosin; × 900.

B, numerous amebas filling the sinusoids in the immediate vicinity of an interlobular branch of the portal vein. Hematoxylin and eosin; × 400.

of degeneration and necrosis which gradually increased in severity toward the central portions of the hepatic lobules (fig. 3 *A*). In these regions of greater necrosis larger numbers of amebas were present in

the sinusoids and in the interstitial spaces. In some areas amebas completely filled the sinusoidal lumens and replaced the adjacent liver cells (fig. 3*B*). A conspicuous finding was the total absence of local infiltration of inflammatory cells in some areas of extreme hepatic cell destruction (fig. 3*B*). More often, however, scattered neutrophilic

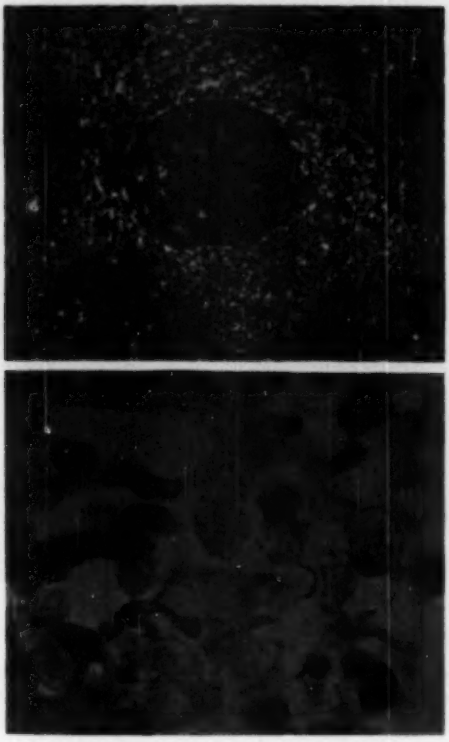

Fig. 3.—*A*, thrombosis of a central vein located in a necrotic hepatic lobule. Amebas were seen in the thrombus and in the tissues surrounding the thrombosed vein. Hematoxylin and eosin; × 100.

B, numerous amebas in contact with the hepatic cells, many of which are being replaced by the parasites, without evidence of inflammatory reaction. Hematoxylin and eosin; × 950.

granulocytes, lymphocytes and macrophages were present in the areas of amebic invasion. Gram and Giemsa stains revealed no bacteria. In many lesions an unidentified substance designated as "basophilic material"

(figs. 4 and 5 *A*) was present. This material was homogeneous and intensely basophilic, and appeared as fine and coarse granules or filaments, or as irregular polyhedral masses ranging in size from a fraction of a micron to about 20 microns in main diameter. It failed to react to Von Kóssa's stain for calcium salts. The "basophilic material" was

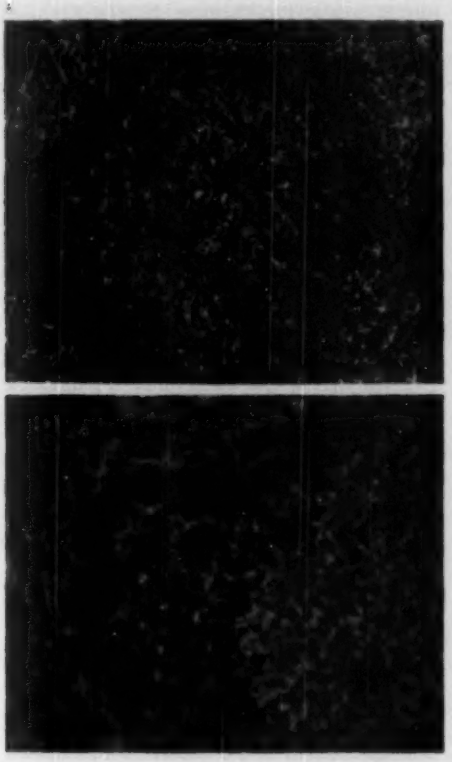

Fig. 4.—*A*, low power view showing the character of the amebic invasion, which progresses from the periphery to the center of the lobule. Note the "basophilic material" on the right side of the field, and the moderate inflammatory reaction. Hematoxylin and eosin; × 100.

B, area of necrosis and amebic invasion showing deposition of "basophilic material." Hematoxylin and eosin; × 200.

generally most abundant in the advancing border of the lesion where the greatest number of hepatic cells were undergoing necrosis and where amebas were numerous. The sinusoids were well preserved at the

periphery of the affected lobules in spite of the presence of amebas within them but were almost totally destroyed from about the midzone to the center of each lobule (figs. 4 *A* and 5 *B*). Reticulum stains showed fragmentation and diminution in the number of reticular fibers in the lesions, most pronounced toward the center of the lobules; yet even in

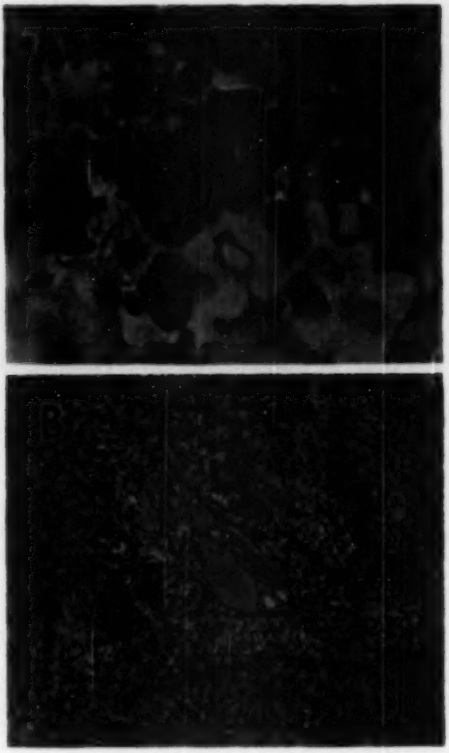

Fig. 5.—*A*, high power view showing the form of some of the larger fragments of the "basophilic material." Amebas and necrotic liver cells are also seen in this field. Hematoxylin and eosin; × 900.

B, low power view of a hepatic lobule showing extensive amebic invasion. Some preservation of the periportal liver cords is evident. Necrosis is more pronounced toward the midzones and central areas. Hematoxylin and eosin; × 100.

regions of total destruction of hepatic cells some reticular fibers persisted (fig. 6 *A* and 6 *B*). Mitotic figures were not observed in the hepatic cells, and there was no evidence of bile duct or fibroblastic proliferation.

The amebas, which were easily recognizable in most instances, showed abundant clear cytoplasm, with occasional formed inclusions. Kupffer's cells were inconspicuous in the necrotic areas. The bile ducts in the portal triads were not affected, and bile canaliculi were not prominent.

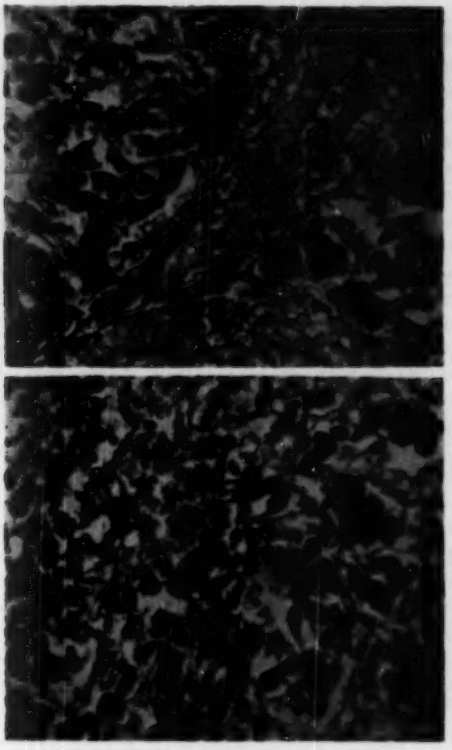

Fig. 6.—*A*, portal space showing preservation of reticular network in spite of thrombosis and amebic invasion of a branch of the portal vein and sinusoids in the immediate vicinity. Snook's reticulum stain; × 450.

B, the reticular fibers around the central vein and adjacent sinusoids are fragmented and partially destroyed. The central vein contains thrombotic material, and there is advanced necrosis of the surrounding hepatic cells. Snook's reticulum stain; × 450.

Absolute identification of the periportal lymphatic channels was not possible in the affected areas. Amebic invasion of the hepatic artery was not observed.

COMMENT

Gross Lesion.—The shape and appearance of the affected areas clearly suggested their vascular origin; grossly they resembled infarcts. Of the possible routes of amebic extension from colon to liver,[15] namely directly through the peritoneal cavity, by way of the lymphatic vessels and by way of the portal blood stream, the last is generally accepted as the most probable. The hepatic artery is logically excluded when it is realized that in order for amebas to enter the systemic arterial circulation from the colon they would first have to pass through the liver and the lungs. However, instances of probable arterial dissemination, e. g., to the spleen, have been reported.[5b] In the present study the parasites were not found in the branches of the hepatic artery but were present in branches of the portal vein.

Thrombosis.—Wherever amebas were seen in one of the large branches of the portal vein, there were small collections of fibrin filaments and leukocytes in the immediate vicinity, usually adherent to the organisms or surrounding them. It is possible that small thrombi accompany the amebas from the colonic lesions to the liver, or that the amebas, once in the portal blood stream, may serve as foci around which small thrombi develop. Large thrombi were seldom seen in the major branches of the portal vein, but occluding thrombi were often present in the small interlobular veins. These findings confirm those reported by Rogers [5a] and Palmer [6] from human material. Amebas were observed in and around the thrombosed vessels and extending toward the center of the lobule. Occasionally, in the very center of a necrotic area there was a thrombosed central or collecting vein, with amebas in the thrombus. The propagation of the thrombi had probably progressed in the direction of the blood flow from the periphery toward the center of the lobule.

Zonal Changes.—It was noted that the hepatic cells, the sinusoids and the reticulum in the periportal zones were better preserved than in the midzones or central areas, even though amebas were present in the periportal sinusoids and some of the interlobular branches of the portal vein were thrombosed. This can be explained on the basis of the unique circulatory arrangements in the hepatic lobule. The finer branches of the hepatic artery enter the sinusoids at the periphery of the lobules,[16] and hence the periportal structures receive a better supply of oxygenated blood.

Inflammatory Reaction.—In some instances of uncomplicated amebiasis of the colon,[17] as well as in some areas of the uncomplicated hepatic

15. Councilman and Lafleur.[5] Rogers,[5] pp. 463 and 596.

16. Maximox, A. A., and Bloom, W.: A Textbook of Histology, Philadelphia, W. B. Saunders Company, 1942.

17. Carrera, G. M., and Faust, E. C.: Am. J. Trop. Med. **29**:647, 1949.

lesions described here, there was an almost total absence of inflammatory reaction. The amebas were seen in intimate contact with degenerating host cells and sometimes had totally replaced them, with no apparent inflammation. When necrosis was extensive, inflammatory infiltration was present, but this may well represent a secondary reaction to the necrotic host tissue itself.

Repair.—Only seven days elapsed between the evident establishment of acute amebic colitis and death. It is unlikely that amebas invaded the portal vein before extensive lesions developed in the bowel. Hence the hepatic lesions were probably not more than 7 days old and possibly less. There was no evidence of encapsulation, fibroblastic proliferation or bile duct or hepatic cell regeneration in or about the lesions at this stage.

SUMMARY

Early amebic hepatitis was observed in 2 kittens with experimental amebic dysentery produced by rectal inoculation of organisms of human origin. Grossly the lesions resembled infarcts. Microscopically there were thrombosis and amebic invasion of intrahepatic branches of the portal vein. In the affected regions the hepatic lobules showed central necrosis and invasion by amebas. There were no signs of hepatic regeneration or fibroblastic proliferation, and inflammatory cellular infiltration was minimal.

VARICELLA PNEUMONITIS

Report of a Case with Autopsy Observations

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DEATHS of chickenpox are rare, and a survey of the available literature, moreover, reveals an even greater rarity of autopsy reports of these cases. This paper concerns itself with the autopsy observations in a case of varicella in which the patient, a woman, died in the acute phase of the disease.

In a review of 2,534 patients hospitalized for varicella, Bullowa and Wishick [1] discovered complications in 5.2 per cent, with a mortality of 0.4 per cent. Twenty-one patients had pneumonia, and 3 others had empyema associated with pneumonia. Other pyogenic complications were common, and Streptococcus hemolyticus was usually cultured from the blood, the respiratory tract or other foci of infection. Of 11 deaths, 7 were due to septicemia and 1 to empyema. One of the 7 patients dying of septicemia had pneumonia as the source of infection. Autopsy findings were not reported in detail in this article, but Waring, Neuberger and Geever [2] learned from the pathologist who examined 8 of these deaths that in all postmortem studies slight to severe lobular pneumonia was found and that none of the lungs showed characteristics of virus pneumonia.

In a series of 775 patients hospitalized with chickenpox Mitchell and Fletcher [3] reported 4 with bronchopneumonia. None of these died. Shuman [4] also noted nonfatal pneumonia in several of 2,200 patients with chickenpox.

We have been able to find only 6 previous autopsy reports of varicella in the literature accessible to us.

In one of these Johnson [5] described a 7 month old infant who died of hydrocephalus and sinus thrombosis at the height of the eruptive stage of chickenpox. He found multiple foci of degeneration in many tissues

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1. Bullowa, J. G. M., and Wishick, S. M.: Am. J. Dis. Child. **49**:923, 1935.
2. Waring, J. J.; Neuberger, K., and Geever, E. F.: Arch. Int. Med. **69**:384, 1942.
3. Mitchell, A. G., and Fletcher, E. G.: J. A. M. A. **89**:279, 1927.
4. Shuman, H. H.: Am. J. Dis. Child. **58**:564, 1939.
5. Johnson, H. N.: Arch. Path. **30**:292, 1940.

(skin, esophagus, pancreas, liver, renal pelvis, ureters, bladder and adrenal glands). This process involved epithelial cells primarily but vascular and lymphatic endothelial cells and histiocytes as well. The acinous cells of the pancreas and the cells of the cortex and medulla of the adrenal gland were affected. The changes consisted in ballooning of the cells and vacuolation of both the cytoplasm and the nucleus. Intranuclear inclusion bodies similar to those that we shall describe were frequent in all these structures.

In a report concerning an 11 day old infant Oppenheimer [6] described widely disseminated visceral lesions with a predilection for epithelial structures. Inclusion bodies were demonstrated in the skin, the esophagus, stomach and intestines, the renal tubules, the pulmonary alveolar septal cells and Hassall's corpuscles of the thymus. There were multiple foci of necrosis in these organs as well as in the spleen and the bone marrow. The blood vessels were often necrotic, giving rise to hemorrhages and thromboses. Oppenheimer mentioned a similar report by Schleussing [7] concerning 3 week old twins with focal necroses of liver, adrenal glands and spleen, but no inclusion bodies were mentioned.

Lucchesi, LaBoccetta and Peale [8] reported an autopsy on a 12 day old infant whose mother contracted chickenpox at term. They, too, saw multiple foci of necrosis in the skin, the lungs, the liver and the gastric mucosa. The lungs were involved by an interstitial pneumonitis with an inflammatory exudate, largely of lymphocytes with a few large mononuclears. Some of the large mononuclears in the alveoli assumed the appearance of desquamated septal cells. Intranuclear inclusion bodies were located in the skin, the lung and the hepatic cells.

Waring, Neuberger and Geever [2] presented the first detailed account of a varicella pneumonitis. Their observations were made on a 40 year old man. There was a cellular exudate in the lungs consisting predominately of large mononuclear phagocytes and rare neutrophilic granulocytes. Some of the alveoli were lined by cuboidal or columnar epithelium, and the septal cells were swollen. The impression was that both the lining alveolar cells and the phagocytes were derived from septal cells. Areas of focal necrosis with arteriolitis and hemorrhagic and fibrinous exudation were prominent. Acute encephalitis and nephrosis were other visceral lesions in this case. Intranuclear and intracytoplasmic inclusions were found only in the tracheal epithelium.

An autopsy on a 32 year old woman dying of varicella pneumonitis was reported by Claudy.[9] The lung showed focal areas of consolidation

6. Oppenheimer, E. H.: Bull. Johns Hopkins Hosp. **74**:240, 1944.
7. Schleussing, H.: Verhandl. d. deutsch. path. Gesellsch. **22**:288, 1927.
8. Lucchesi, P. F.; LaBoccetta, A. C., and Peale, A. R.: Am. J. Dis. Child. **73**:44, 1947.
9. Claudy, W. D.: Arch. Int. Med. **80**:185, 1947.

due to exudation of fibrin and leukocytes, few of which were segmented granulocytes. Hyaline membranes and foci of necrosis also occurred. The liver and the spleen contained foci of necrosis, and intranuclear inclusions were present in the hepatic cells and questionably in the skin.

In addition to these cases in which autopsies were made, a number of clinical reports have appeared dealing with pneumonia, encephalitis, nephritis and nephrosis as complications of chickenpox. Occasionally, two or more organs were involved in the same patient.

REPORT OF CASE

A 34 year old housewife was admitted to Porter Hospital in Middlebury, Vt., on March 11, 1950, in extreme respiratory distress and died soon after admission.

The deceased was the mother of two children, one of whom had recently recovered from chickenpox and the other of whom was at the time undergoing an uneventful siege of the same disease. Varicella was epidemic in the area at this time, but no deaths had been reported.

The past history was noncontributory except for frequent asthma-like attacks a year before, relieved by sterile hypodermic injections.

A generalized papular eruption had appeared on March 5, at which time the subject was only mildly ill. Two days later pustules and vesicles appeared on the face and torso. On the fourth day of illness a frequent cough with production of copious tenacious blood-tinged sputum became manifest. Although she had been fairly well until this time, the patient was now rather dyspneic and had a temperature of 102 F. Administration of penicillin was started. On the following morning the patient's temperature, pulse rate and blood pressure were within normal limits, but the facial lesions had become hemorrhagic. On that afternoon dyspnea increased remarkably, and cyanosis appeared. She was admitted to the hospital and death occurred shortly afterward, on the sixth day of illness.

Autopsy (seventeen hours after death).—External Examination: The body was well developed and well nourished. Numerous superficial discrete lesions were present in decreasing order of frequency on the face, neck, upper part of torso, lower part of torso, arms and thighs, and forearms. They consisted of reddish purple papules, large, nonumbilicated vesicles, measuring up to 1.0 cm. in their largest diameter, and ruptured vesicular lesions, many with a hemorrhagic base. The hemorrhagic lesions existed only on the face and showed a tendency to confluency. The vesicles were located entirely on the neck. There were no macules, pustules or crusts, and neither erythema nor induration was noted around the lesions.

The lips and the nail beds were cyanotic. The nostrils and the oral cavity were filled with frothy brownish fluid. Postmortem rigor prevented further examination of the oral cavity. There were no palpable lymph nodes and no edema.

Internal Examination: Each pleural cavity contained about 200 cc. of thin, watery brownish fluid. The left lung weighed 730 Gm. and the right lung 770 Gm. The lungs were similar in appearance, and pathologic involvement was uniform throughout. The surfaces were smooth and reddish purple, with occasional bright hemorrhagic patches but with no fibrinous or purulent exudate. The lungs were somewhat firm but still moderately crepitant. On section they were frothy and mottled pink and red. The major bronchi were reddened and contained a small amount of a hemorrhagic exudate.

The pericardial and abdominal cavities revealed nothing of note. The heart weighed 212 Gm. and showed moderate dilatation of the right ventricle and auricle.

The myocardium was generally flabby. Numerous ulcers, measuring up to 1.0 cm. in diameter, with a necrotic base, covered the entire length of the esophagus. The spleen weighed 110 Gm. and it, together with the rest of the gastrointestinal tract and the liver, pancreas, kidneys, bladder and genital organs, were grossly normal. The brain was not examined.

Microscopic Examination.—Skin: The papular lesions showed localized areas, in the stratum Malpighii (stratum germinativum), of swelling and vacuolation of the cell nuclei and, to a lesser extent, the cytoplasm. The chromatin was clumped in the center of the vacuolated nucleus but ultimately was disposed at the periphery, leaving a large clear center. The nuclei thereby assumed a ballooned appearance.

With the coalescence of the vacuolated cells, multiloculated and, finally, large uniloculated vesicles were formed in the stratum Malpighii (fig. 1). The locules were separated by strands of elongated, giant epithelial cells which radiated out-

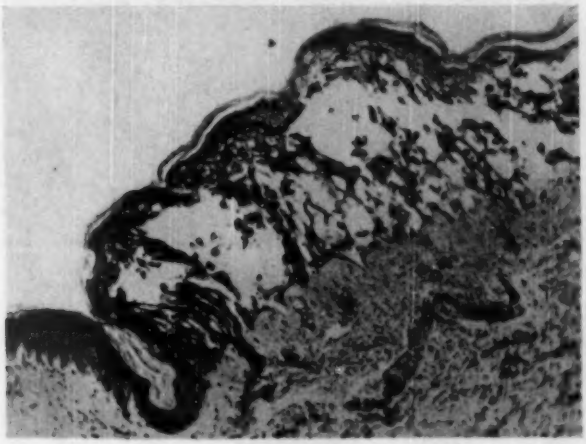

Fig. 1.—Skin vesicles. Hematoxylin and eosin; × 100.

ward from the base to the surface. In the larger vesicles the germinal layer of the epithelium was no longer seen, and ballooning of the nuclei of the stratum lucidum was in evidence, but this layer remained intact. Lying freely within the larger vesicles were large, swollen, degenerated epithelial cells which formed rounded eosinophilic hyaline bodies. Bizarre and multinucleated giant cells and occasional neutrophilic granulocytes were also found within the vesicles. Large, rounded, pink intranuclear inclusion bodies occurred in rare ballooned epithelial cells lying in the skin vesicles.

A third type of lesion was represented by large ulcers of the epidermis with necrosis of the base extending through the entire thickness of the dermis. Remnants of necrotic squamous epithelium were seen on the base of the ulcers.

Mild to moderate capillary congestion was found within the dermis underlying all types of lesions. The skin appendages were free of pathologic change. None of the hemorrhagic lesions were removed for section, since they were all on the face.

Lungs: All sections showed similar features of severe widespread inflammatory changes.

One of the most prominent findings was that of multiple, fairly large foci of fibrinous exudation filling the alveoli (fig. 2*A*), while elsewhere the same

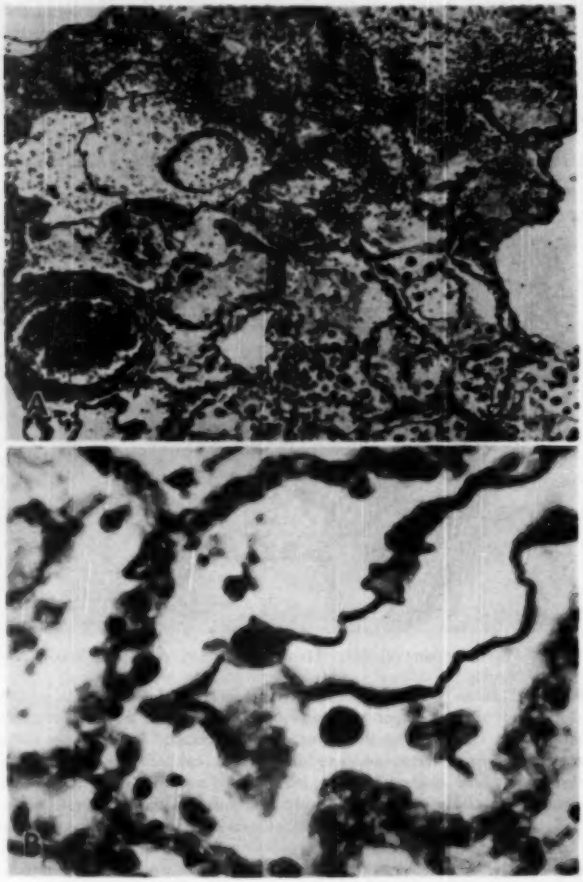

Fig. 2.—*A*, lung showing fibrinous exudation, hyaline membranes, necrosis and large mononuclear phagocytes. Hematoxylin and phloxine; × 100. *B*, lung showing swollen, proliferated septal cells. Hematoxylin and eosin; × 475.

process was diffuse. In many areas the fibrin was condensed along the alveolar walls to form hyaline lining membranes. A good deal of granular debris was also found within the alveoli.

The cellular exudate was chiefly mononuclear. Macrophages were present in large numbers within the alveoli and were often huge and multinucleated; many were laden with hemosiderin pigment. The septal cells were moderately swollen and hyperplastic (fig. 2*B*), and they often appeared as a continuous layer of cells lining the alveoli. Frequently, rounded and polyhedral cells lay within the alveoli, seeming to take origin from the septal cells by desquamation. They contained no pigment, but apparently it was from these cells that the large intra-alveolar phagocytes arose. Neutrophilic granulocytes were in general inconspicuous and were found only within the septums in most areas.

Numerous areas of necrosis were irregularly distributed throughout the lung. A hemorrhagic fibrinous exudate with a mild to moderate infiltration of neutrophilic granulocytes marked these areas. The alveolar cells were necrotic, but the alveolar outline was still faintly visible, and there was no tendency toward suppuration. The arteries in these areas were also involved in the necrotic process. The bronchioles showed severe desquamation of the lining epithelium, but the lumens contained only a slight amount of edema fluid.

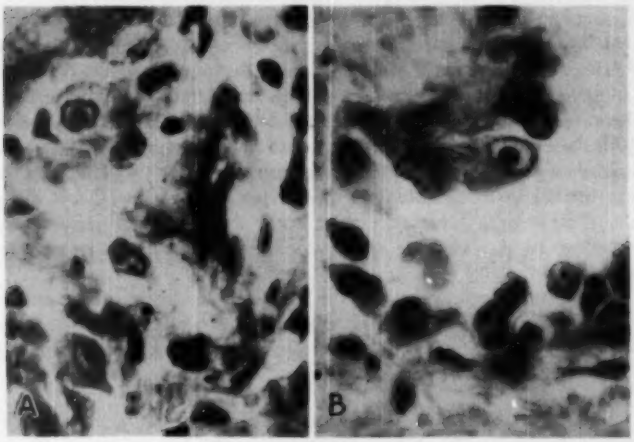

Fig. 3.—*A*, intranuclear inclusion bodies in two intra-alveolar "septal" cells. Hematoxylin and phloxine; × 900. *B*, intranuclear inclusion body in bronchiolar epithelial cells. Hematoxylin and eosin; × 900.

Gram stains of the lung sections revealed no bacteria.

Large, rounded, well defined, pink intranuclear inclusion bodies occurred quite frequently within the desquamated septal cells and in an occasional nondesquamated septal cell and bronchiolar epithelial cell (fig. 3). These inclusions were seen equally well with both the hematoxylin and eosin and the phloxine and hematoxylin stain.

Other Viscera: Of the remaining organs, only the spleen and the esophagus showed significant changes. There were numerous shallow ulcers of the esophageal mucosa with chronic inflammation of the submucosa. The malpighian corpuscles of the spleen exhibited small foci of necrosis, which were also seen to a slight extent

in the pulp. No specific inflammatory changes were observed in the epithelial elements of organs other than the skin and the lungs.

COMMENT

It is evident that in occasional instances varicella may give rise to visceral complications, notably in the lung, the brain and the kidney; and it shows a tendency, particularly in infants, to involve epithelial structures throughout the body, associated with focal necroses.

The changes found in the lung in varicella pneumonitis are those usually seen in other types of virus pneumonia with the addition of characteristic intranuclear inclusion bodies in the septal cells and bronchiolar epithelial cells. Other features consistently noted in various reports are swelling, proliferation and desquamation of the septal cells to form large phagocytes, which are the usual cellular exudate. Neutrophilic granulocytes are rare, and foci of necrosis, hemorrhage and fibrinous exudation occur with regularity. Arteriolitis is also described. The general picture is that of a patchy bronchopneumonia with areas of consolidation and a tendency toward confluency without suppuration. With the exception of the characteristic intranuclear inclusions, none of these changes are peculiar to varicella pneumonia, for they have all been seen in various combinations in other types of virus pneumonia, influenzal pneumonia, acute rheumatic fever and radiation pneumonitis, according to a review of this subject by Waring, Neuberger and Geever.[2]

The hemorrhagic lesions of the skin seen in this case are another complication which has been described infrequently. Cohen and Bansmer [10] and a few others have proved in similar circumstances that the underlying pathologic condition was thrombopenic purpura.

SUMMARY

Autopsy observations on varicella pneumonitis in an adult are presented. The lesions of the skin and the lung are described in detail, and previous cases of chickenpox in which autopsies were made are reviewed.

10. Cohen, J. J., and Bansmer, C.: New England J. Med. **273**:222, 1947.

Case Reports

A PARTIALLY HEALED PRIMARY LESION IN A CASE OF GENERALIZED HISTOPLASMOSIS

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SINCE the original observations of Palmer [1] and of Christie and Peterson [2] there has accumulated a body of evidence which indicates that in certain regions histoplasmosis may be the major cause of pulmonary calcifications in tuberculin-negative persons. Most of the evidence, however, has been more or less circumstantial in nature and is based on the observation that such persons frequently show positive skin reactions to histoplasmin. Furcolow, Mantz and Lewis [3] reported that uncalcified pulmonary lesions, so-called "soft" infiltrates, could often be found roentgenologically in tuberculin-negative, histoplasmin-positive children. By following these cases they were able to demonstrate [4] progressive calcification of the lesions.

These indications of an apparently benign, localized form of the disease which had previously been known only as a disseminated, fatal infection have led gradually to the concept of a "primary" localized infection, which usually heals with calcification, and a less common, "secondary," disseminated form. There would appear to be, then, a parallelism between the course of this disease and that of tuberculosis. Although calcification was frequently observed in the hilar lymph nodes in the earlier roentgenologic studies, and large caseous nodules in the lungs at autopsy,[5] there have, as yet, been no pathologic reports emphasizing a typical primary complex analogous to that found in tuberculosis. The case reported here presents such a partially healed primary complex due to Histoplasma capsulatum, associated with disseminated, fatal histoplasmosis.

From the Department of Pathology, Washington University School of Medicine.

1. Palmer, C. E.: Pub. Health Rep. **60**:513, 1945.

2. Christie, A., and Peterson, J.: Am. J. Pub. Health **35**:1131, 1945.

3. Furcolow, M. L.; Mantz, H. L., and Lewis, I.: Pub. Health Rep. **62**:1711, 1947.

4. Furcolow, M. L.: Pub. Health Rep. **64**:1364, 1949.

5. Kuzma, J.: Dis. of Chest **13**:338, 1947. Dublin, W. B.; Culbertson, C. G., and Friedman, H. P.: Am. Rev. Tuberc. **58**:562, 1948.

HISTORY OF CASE

On Feb. 26, 1950 a 6 month old white boy was admitted to St. Louis Children's Hospital with a history of enlargement of the liver and the spleen of two months' duration. It was stated that the child had done fairly well after a normal birth until the age of 2 months, at which time he began to eat poorly, and distention of the abdomen was noted. The family physician examined the child and changed his formula, whereupon his condition improved. At the age of 4 months he was again brought to the physician with similar complaints. Examination revealed that liver and spleen were greatly enlarged, and the child was referred to a near-by hospital. Here the bone marrow was reported as essentially normal. A diagnosis of nutritional anemia was made, and several blood transfusions were given. During the following month at home the child had several febrile periods in which his temperature reached 104.5 F. He was returned to the hospital, where he continued to have fever with progressively increasing anemia during the next month until he was transferred to the St. Louis Children's Hospital.

Physical examination on admission showed a poorly nourished infant, weighing 4.9 Kg. The abdomen was frankly protuberant. The skin was loose and dry but not jaundiced. The cervical, axillary and inguinal lymph nodes were moderately enlarged and firm. Ears, eyes, nose, oral cavity and throat were all normal. The heart and the lungs appeared normal. The spleen extended 8 cm. and the liver 5.5 cm. below the costal margins in the midclavicular lines. Both were firm and smooth and apparently nontender. The results of a neurologic examination were within normal limits.

The red blood cell count was 4,200,000 per cubic millimeter, the concentration of hemoglobin 10.5 Gm. per hundred cubic centimeters, and the white blood cell count 4,800, with a moderate shift to the left. The urine showed no abnormalities. The Kline test was negative. The lung fields were reported as clear on roentgenologic examination.

The sternal marrow revealed hypocellularity and clumps of histoplasma organisms, both in and outside cells. Culture of the marrow yielded a heavy growth of H. capsulatum. Skin tests with tuberculin, histoplasmin (1:1,000), blastomycin and coccidioidin all gave negative results. The child's father, mother and two sisters, aged 5 and 12 years, all showed positive skin reactions to histoplasmin. A third sister, 14 years old, did not show a positive skin reaction.

In treatment, blood transfusions and antibiotics were given, without response. Severe diarrhea developed on the fourth hospital day. On the sixth day antibiotics were withdrawn, and petechiae were first noted over the abdomen. By the sixteenth hospital day the entire trunk and parts of all the extremities were covered by purpuric spots. The next day gross hematuria appeared. The child's condition became progressively worse, and he died eighteen days after admission. His temperature had ranged between 38 and 39 C. (100.4 and 102.2 F.) during the time that he was in the hospital.

PATHOLOGIC OBSERVATIONS

Autopsy (four hours after death).—The examination was limited to the thorax and the abdomen. The body was that of an emaciated 6 month old white male infant. The skin of the extremities and of the protuberant abdomen, as well as the mucous membranes of the mouth, contained many scattered and confluent petechiae. There was moderate

enlargement of the superficial lymph nodes. The peritoneal cavity contained 50 cc. of clear yellowish fluids, and the pericardial sac 3 cc. of similar fluid. The pleural cavities did not contain free fluid.

The heart weighed 27 Gm. and was not abnormal in appearance. The reddish brown thymus weighed 3 Gm. and revealed no gross lesions.

Together the lungs weighed 100 Gm. The pleural surfaces contained many punctate hemorrhages, as well as larger hemorrhagic areas which were nodular to touch. The posterior portions of the lower lobes of both lungs were dusky purple, depressed and noncrepitant. The cut surfaces were moist and revealed scattered firm hemorrhagic nodules, 0.5 to 1 cm. in diameter, which contained 2 to 3 mm. centers of soft, gray, necrotic material. In the apex of the upper lobe of the right lung were several confluent nodules with firm gray translucent shells and bright yellow pasty centers. The aggregate nodule measured 8 mm. in diameter. One of the superior tracheobronchial lymph nodes on the right was greatly enlarged, measuring 1 cm. in diameter. On cutting, it was found to be firm and slightly gritty and to contain several confluent nodules with yellow pasty centers, which almost filled the node. The other hilar and mediastinal nodes were moderately enlarged but did not contain nodules.

The liver was enlarged, weighing 415 Gm., compared with a normal weight of 200 Gm. Beneath the capsule and scattered in irregular groups on the cut surfaces were myriads of tiny yellowish dots a millimeter or less in diameter. Mingled with these were many punctate hemorrhages. The hepatic parenchyma itself was brownish. The gallbladder and the pancreas were not unusual.

The firm, dark purple spleen weighed 271 Gm., 17 Gm. being the average normal weight. The cut surfaces were smooth and homogeneous in appearance, with a few scattered yellow flecks.

The right and left kidneys weighed 31 and 33 Gm., respectively. The capsules stripped easily, revealing smooth lobulated surfaces. On the external as well as on the cut surfaces of both kidneys were widely scattered yellowish gray dots a millimeter or less in diameter. These flecks were present in both cortex and medulla. Otherwise the kidneys were not unusual in appearance. The remainder of the genitourinary tract was normal.

Each adrenal gland weighed 2.5 Gm. and contained no grossly visible lesions.

The mucosa of the stomach, cecum and ascending colon was reddened and contained many petechiae. In the cecum there were also small gray patches, about 1 mm. across, visible through the mucosa. The remainder of the intestinal tract was normal.

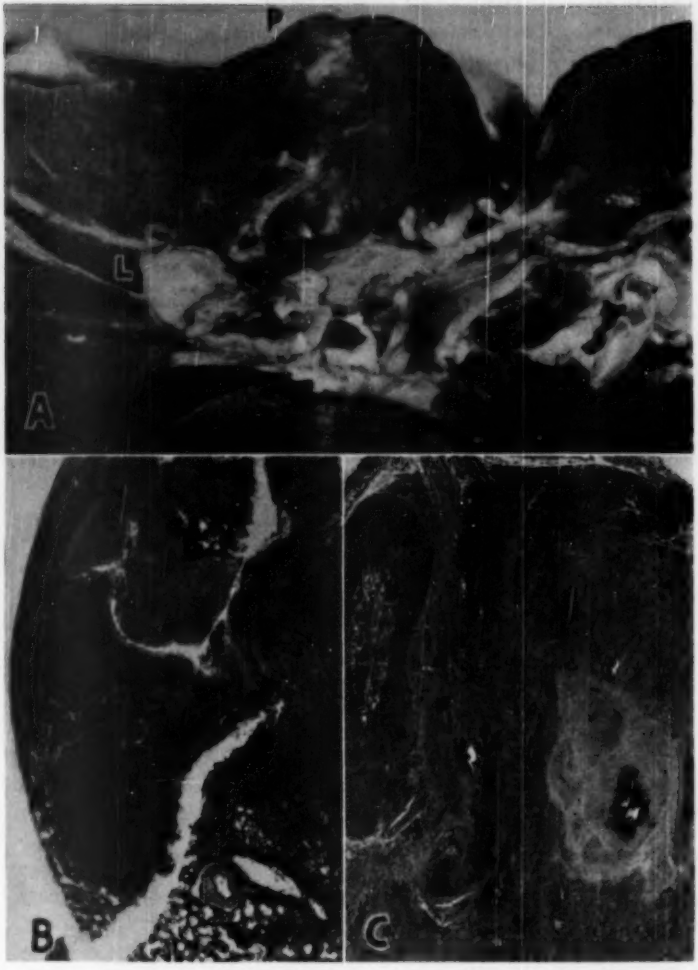

Fig 1.—*A*, gross appearance of lung with a peripheral nodule (*P*) and a nodule in a tracheobronchial lymph node (*L*). *B* and *C*, low magnifications showing the caseous nodules with their calcific centers (*B*) in the lung and (*C*) in the lymph node.

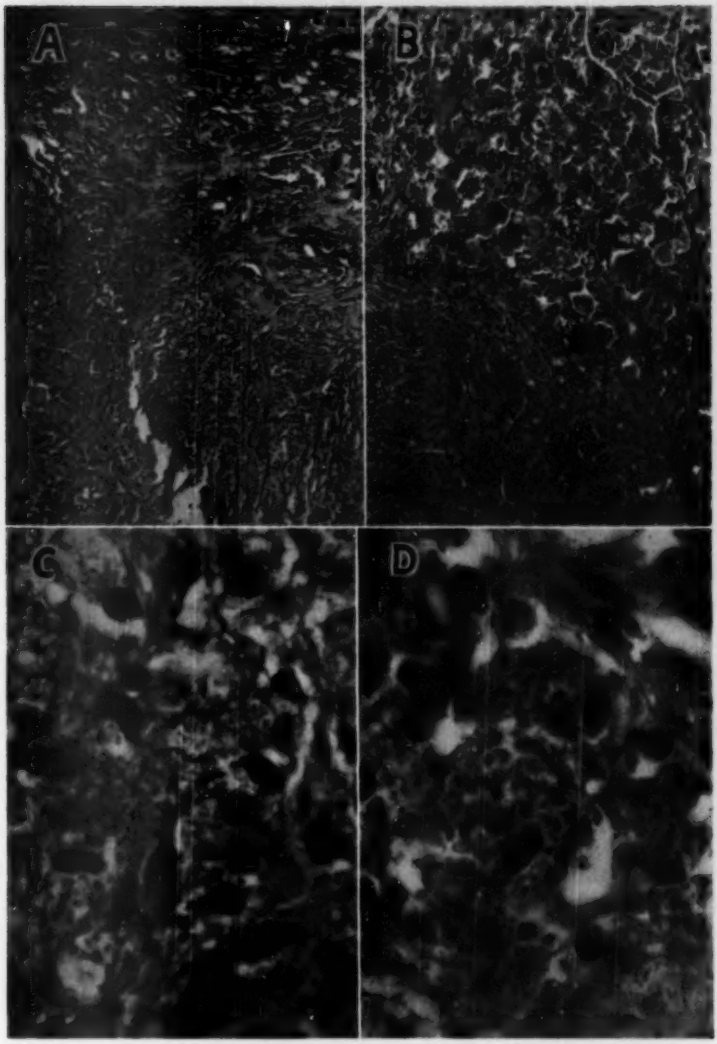

Fig. 2.—*A* and *B*, proliferative reactions at the edge of the caseous nodule in the lung (*A*) and the lymph node (*B*); × 120.

B and *C*, large mononuclear cells filled with organisms at the edge of the nodule in the lung (*C*) and the lymph node (*D*); × 1080.

The portahepatic, periaortic and mesenteric lymph nodes were moderately enlarged and contained yellowish foci on cut section.

Microscopic Examination.—Smears of the peripheral blood made at the time of autopsy and stained with Wright's stain showed many organisms, both inside and outside cells.

The confluent nodules in the apex of the right lung were found to contain centers of acidophilic material with a ground glass appearance. In the middle of the largest of these was a moderate deposit of calcific material. Around this necrotic center in a typical nodule was a wide area in which the alveolar pattern was obliterated by masses of large mononuclear cells filled with the yeastlike form of Histoplasma, together with proliferating fibroblasts. There was a fairly sharp line of demarcation between this zone and relatively normal lung, in which the alveolar walls were thickened by distended capillaries and the alveoli contained a few cells with organisms and occasional mononuclear cells and red blood cells.

Scattered throughout the remainder of both lungs were small foci of intense mononuclear infiltration which centered either around several organism-filled cells or around a small focus of caseous necrosis. There were also larger areas in which the normal structure was obliterated by masses of necrotic debris containing karyorrhectic nuclei and colonies of gram-positive bacteria. The alveoli surrounding these zones contained edema fluid and large numbers of segmented granulocytes and red blood cells.

Sections of the right tracheobronchial lymph node showed nodules with much the same histologic appearance as those described in the lung, that is, a partially calcified caseous center surrounded by sheets of large cells filled with organisms and some intermingled fibroblasts. The normal structure of the node was almost completely destroyed. Stains for acid-fast organisms on both the lung and the lymph node sections revealed none.

In the liver were numerous foci about the size of a hepatic lobule which were made up of small groups of large organism-laden cells surrounded by mononuclear cells, fibroblasts and many red blood cells. Some of these foci were confluent. The liver otherwise was not abnormal except that the Kupffer cells were distended by organisms and that organism-filled macrophages were present in the sinusoids.

The sinusoids of the spleen were greatly distended by red blood cells and large numbers of organism-containing cells. No focal lesions were seen, however. The malpighian bodies were small and widely separated.

In both the cortex and the medulla of the kidneys there were scattered areas of necrosis containing bacterial colonies. These were surrounded by masses of segmented granulocytes, many of which had karyorrhectic nuclei. Elsewhere the tubular epithelium was swollen

and the cytoplasm coarsely granular. The glomeruli were not unusual except for the presence of organism-filled cells in some of the capillary tufts.

The mucosal pattern of the colon was altered by the presence of many cells containing organisms. In the submucosa these cells tended to be grouped in foci surrounded by smaller mononuclear cells and some extravasated red cells.

The structure of several mesenteric nodes was almost entirely destroyed by masses of organism-containing cells and proliferating fibrous tissue, which tended to form whorls about the groups of these large cells.

Besides numerous isolated cells containing organisms scattered throughout the cortex and medulla of the adrenal glands, there were several small foci made up of these cells, closely packed together, in the cortex of both glands. There was no cellular reaction around these foci.

The thymus had the histologic appearance of involution. There were also present, in groups of varying size, the large, organism-laden cells.

The sternal and vertebral marrow showed normal over-all cellularity, with the erythroid cells more numerous than usual. There appeared to be about the usual number of megakaryocytes. There were numerous clumps of organisms outside cells as well as within large mononuclear cells.

Sections of heart, pancreas, skin, testis and prostate showed no significant histologic abnormalities except for occasional isolated organism-containing cells in the connective tissues or in blood vessels.

BACTERIOLOGIC EXAMINATION

H. capsulatum was isolated from the heart's blood, the spleen, a lung, an adrenal gland and a mesenteric lymph node. Bacterial culture also yielded Micrococcus albus (hemolytic) and Escherichia coli from all these tissues, as well as Pseudomonas aeruginosa from the lung.

COMMENT AND SUMMARY

A case of fatal disseminated histoplasmosis in an infant has been presented. The most striking feature of this case was the partially calcified caseous nodules found in a lung and a tracheobronchial lymph node, analogous to the primary complex of tuberculosis. This case gives anatomic evidence that Histoplasma may enter by the respiratory tract and produce primary lesions in the lung and draining lymph nodes, which may heal with calcification.

AORTIC ATRESIA, MITRAL STENOSIS, HYPOPLASIA OF THE LEFT VENTRICLE AND OTHER CARDIAC ANOMALIES IN NEWBORN

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AND
JOHN B. MIALE, M.D.
MARSHFIELD, WIS.

THE DIAGNOSIS of congenital lesions is assuming an ever more important role in cardiology. Among the conditions in the cyanotic group there are some for which the prognosis is good and the results of corrective surgical procedures encouraging. Other conditions, such as the one reported here, must be differentiated because the prognosis is extremely poor and because an accurate diagnosis is of great help to the physician and comfort to the family.

In Abbott's atlas of congenital heart disease [1] only 12 cases are presented featuring the combination of aortic atresia, hypoplasia of the ascending aorta, mitral stenosis, hypoplasia of the left ventricle and patent ductus arteriosus and foramen ovale. We have been able to locate 4 additional cases [2] of this nature and are reporting a fifth, making a total of 17.

REPORT OF A CASE

A primipara with a normal pregnancy gave birth to a 7 pound, 10 ounce (3,175 Gm.) boy on Jan. 19, 1949 after a rapid but otherwise uneventful labor. The infant cried at once after birth and appeared to be completely normal. Fifteen hours after delivery he had a slight cyanotic hue, which disappeared with oxygen therapy. Five hours later, respiratory distress and cyanosis were again present, only to leave after oxygen therapy. A short time later, however, approximately twenty-four hours after birth, the infant suddenly became ashen gray and died.

AUTOPSY

The necropsy was performed seven hours post mortem. The skin, the mucous membranes and the nail beds were markedly cyanotic. The sagittal suture was fused, and the posterior fontanel measured only 2 mm. in its greatest diameter. Other findings of note were limited to the heart and the great vessels.

The heart was in its normal position, but it gave off only one large arterial trunk, which measured 8 mm. in diameter (fig. 1). The right

From the Department of Pathology, St. Joseph's Hospital and the Marshfield Clinic.

1. Abbott, M.: Atlas of Congenital Cardiac Disease, New York, American Heart Association, 1936.

2. Rossman, J. I.: Am. J. Dis. Child. **64**:873, 1942. Anderson, N. A., and Sano, M. E.: Ibid. **62**:629, 1941. Popjak, G.: J. Path. & Bact. **54**:67, 1942. Isaacson, N. H.; Spatt, S. D., and Grayzel, D. M.: J. Pediat. **29**:22, 1946.

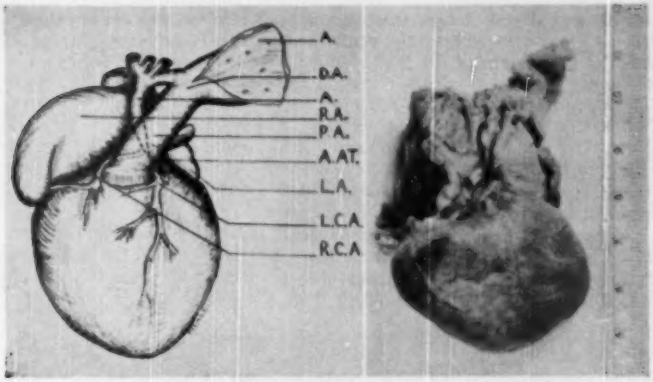

Fig. 1.—Anterior view; diagrammatic drawing and photograph. *A.* indicates the aorta; *D.A.*, the ductus arteriosus; *R.A.*, the right auricle; *P.A.*, the pulmonary artery; *A.AT.*, the atretic aorta; *L.A.*, the left auricle; *L.C.A.*, the left coronary artery; *R.C.A.*, the right coronary artery. The scale shows centimeters.

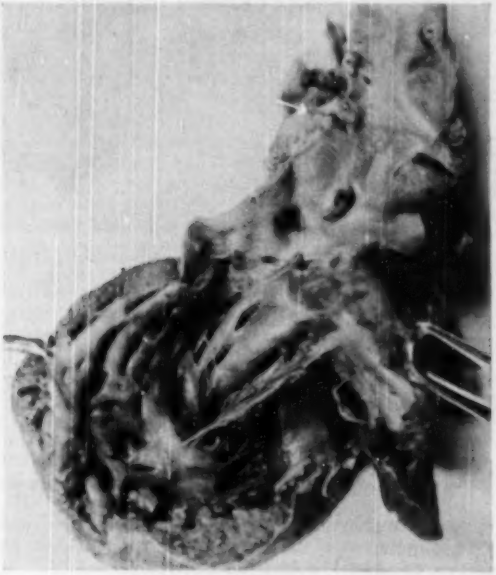

Fig. 2.—Opened specimen; × 1.5. The interior view includes the large right ventricle, the tricuspid valve and the pulmonary arterial trunk. The small aorta enters the trunk from the side, as shown by the arrow.

auricle was slightly larger than normal and received the venae cavae in the usual manner. The right ventricle was relatively huge, making up most of the weight of the heart, with its wall measuring 5 to 6 mm. in thickness (fig. 2). A normal tricuspid valve separated it from the auricle. The circumference at the pulmonary valve was 21 mm., and the artery had its origin from this single ventricle. The right pulmonary artery was given off 4 mm. above the pulmonary valve, while 2 mm. distally was the origin of the left. The left auricle was small but received four pulmonary veins. This chamber freely communicated with the right auricle through a patent foramen ovale 11 mm. in diameter.

The mitral orifice was extremely small, measuring 1 mm. in diameter. It led into an aplastic left ventricle located entirely within the wall of the right ventricle. The greatest transverse diameter of the aplastic ventricle was only 3.5 mm., while its depth from the mitral leaflets to the apex

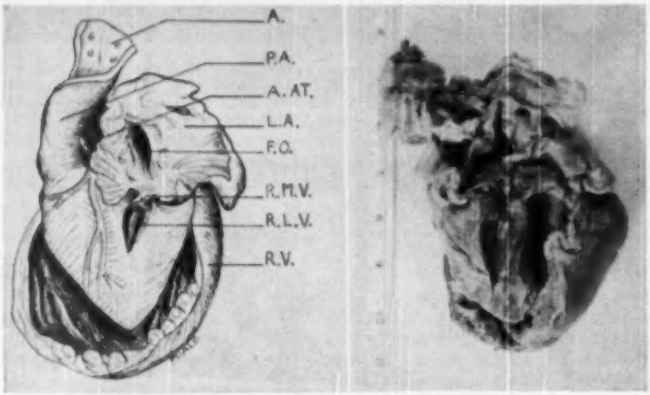

Fig. 3.—Posterior view; diagrammatic drawing and photograph. *A.* indicates the aorta; *P.A.*, the pulmonary artery; *A.AT.*, the atretic aorta; *L.A.*, the left auricle; *F.O.*, the foramen ovale; *R.M.V.*, the rudimentary mitral valve; *R.L.V.*, the rudimentary left ventricle; *R.V.*, the right ventricle.

was 6 mm. There was no orifice other than that at the mitral valve. The aorta at its origin was completely atretic and in the remainder of its first portion was hypoplastic. The two coronary arteries arose a few millimeters above the blind proximal end of the aorta, at which point the vessel had a diameter of 1.5 mm. This hypoplastic structure continued cephalad for 21 mm., at which point it joined a widely dilated patent ductus arteriosus. The ductus was 9 mm. in length and 4 mm. in diameter (fig. 3).

Microscopic examination of serial sections from the myocardium, including one from the site of the mitral orifice, failed to show any inflammatory reaction or other histologic abnormalities.

The anatomic diagnosis was aortic atresia, hypoplasia of the ascending aorta and left ventricle, mitral stenosis, patent foramen ovale and patent ductus arteriosus.

COMMENT

Congenital cardiac anomalies would appear to be more commonly associated with strictly developmental errors than with infections.

In the case described here no evidence of inflammatory changes was demonstrated. Apparently excessive leaflet tissue or fusion of the valves for some unknown reason resulted in atresia of the aortic valve. The hypoplasia of the aorta and left side of the heart represents the atrophy of disuse, while the enlargement of the side of the heart is hypertrophy of excessive work. The patent foramen ovale and the patent ductus arteriosus were necessary to maintain the altered circulation.

The circulation is not difficult to follow in such a case. Oxygenated blood from the pulmonary veins entering the left auricle passes through the patent foramen ovale to mix with the venous blood of the right auricle. This stream enters the right ventricle through the tricuspid valve and leaves that chamber by means of the pulmonary artery. A portion of the blood reaches the lungs via the right and left pulmonary arteries while the remainder enters the ductus arteriosus and flows thence to the arch of the aorta and the systemic circulation. A retrograde flow down the hypoplastic ascending aorta supplies the coronary arteries.

Recently Taussig [3] reported 2 cases of this general nature in which the diagnosis was made before death. Outstanding clinical features include intense cyanosis, which usually appears shortly after birth, weak pulse, low blood pressure and right axis deviation of the electrocardiogram. Murmurs may or may not be present. Fluoroscopic examination shows a greatly enlarged right ventricle without left ventricular enlargement, a distended pulmonary conus and pulmonary artery, which occupy their normal positions, and a distended right auricle and superior vena cava. Evidence of cardiac failure appears early.

As this condition is not compatible with life for more than a few days, the antemortem diagnosis is of value only for its prognosis. At the present time there is no treatment to aid the mechanically poor heart, and life can exist only for a few days after birth. While antemortem diagnosis is of value only for its hopeless prognosis, that knowledge can be helpful both to the physician and to the family.

SUMMARY

A case of aortic atresia, hypoplasia of the ascending aorta, mitral stenosis, hypoplasia of the left ventricle and patent ductus arteriosus and foramen ovale is presented.

This represents the seventeenth case of this syndrome reported.

The clinical picture of intense cyanosis, weak pulse, low blood pressure and right axis deviation in the electrocardiogram is typical, but the prognosis is very poor, death usually occurring a few days after birth.

3. Taussig, H. B.: Bull. Johns Hopkins Hosp. **76**:75, 1945.

ADRENAL CYSTS

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FEW OBSERVATIONS have been published recently on cysts of the adrenal gland, in contrast to the numerous reports before 1920. Because of this fact and because of the rarity of the condition, the present case is of interest.

REPORT OF A CASE

A 30 year old white woman had been in good health until two years prior to her hospitalization. At that time the finger, knee and ankle joints became painful and swollen. There was no associated fever. The symptoms soon disappeared, leaving no residual damage. The patient remained well until four weeks prior to admission, when there was recurrence of similar symptoms, this time accompanied by an intermittent low grade fever.

The family history and the past history were noncontributory.

Physical examination on admission revealed slightly swollen fingers and knee joints with some limitation of motion. A low grade blowing systolic murmur was heard at the mitral valve area. The heart was not enlarged; the tones were distinct; the blood pressure was 110 systolic and 72 diastolic. The pulse rate was 82 per minute and regular. Diminished breath sounds and dulness to percussion were noted over the base of the left lung posteriorly. A large, smooth mass was palpated in the left upper quadrant of the abdomen, extending from the subcostal margin down to the level of the umbilicus, medially to the midline and laterally to the flank. This mass moved slightly with respiration, but no notch was felt. The liver was not palpable. A few small lymph nodes were found in both axillas and both inguinal areas. A rash was not present.

Roentgenograms of the chest showed fluid at the base of the left lung. A flat roentgenogram of the abdomen and a gastrointestinal series revealed a mass in the left upper quadrant of the abdomen, displacing the stomach to the right of the midline. An electrocardiogram made on admission was normal except for sinus tachycardia.

White blood corpuscle counts ranged from 4,100 to 5,150 per cubic millimeter, with 63 per cent neutrophilic granulocytes, 8 per cent band granulocytes, 26 per cent lymphocytes and 3 per cent monocytes. The red blood corpuscle counts were in the range of 3,240,000 per cubic millimeter, with 9.3 Gm. of hemoglobin per hundred cubic centimeters of blood and a hematocrit reading of 31. The urine showed occasional leukocytes and erythrocytes with a few hyaline and granular casts. The albumin content varied from 1 to 2 plus.

Marrow obtained by sternal puncture revealed the typical Hargrave cell of disseminated lupus erythematosus.

Serologic tests for syphilis and agglutination tests for typhoid, paratyphoid and brucellosis gave negative results. The blood sugar was 74 mg. per hundred cubic centimeters. Blood nonprotein nitrogen was 27 mg., cholesterol 157 mg., creatinine 2.6 mg., total proteins 7.5 Gm., albumin 3.4 Gm. and globulin 4.1 Gm. per hundred

From the Laboratory of the Jewish Hospital.

cubic centimeters. Diastase was 54 Somogyi units; alkaline phosphatase, 3.0 Bodansky units. The icterus index was 2. The cephalin-cholesterol flocculation was 3 plus. Sulfobromophthalein retention was 2 per cent at 45 minutes. The erythrocyte sedimentation rate was 38 mm. in 1 hour. Blood cultures were negative.

The patient's course in the hospital was gradually downhill. She had an intermittent fever, her temperature rising as high as 105 F. Signs of fluid in the base of the left lung increased. Pain, associated with respirations, developed over the xiphoid process, and the patient became dyspneic. The heart tones remained of good quality. The neck veins became distended. The pulse rate rose to 140 per minute, and a paradoxic pulse was felt. The area of cardiac dulness to percussion increased, and a roentgenogram of the chest revealed a larger cardiac shadow than on admission. The blood pressure dropped to 90 systolic and 50 diastolic. Therapy at various times included two blood transfusions and administration of salicylates, penicillin, oxygen, codeine and morphine, all without any response. Pulmonary edema developed. The patient died two weeks after admission. The clinical diagnosis was disseminated lupus erythematosus involving the pericardium, the pleurae, joints, the kidneys and the spleen.

NECROPSY

Gross Observations.—Autopsy was performed four hours after death. Examination of the cranial cavity was restricted. External inspection revealed a well developed, fairly well nourished person with enlarged nodes in both axillary and inguinal regions and a large mass in the left upper quadrant of the abdomen. A hydrothorax of 1,000 cc. of thin, turbid, yellow fluid was present on the left side. In the pericardial cavity 450 cc. of serosanguinous fluid separated the visceral and parietal layers of the pericardium, which were covered with a thick fibrinous deposit. The heart weighed 400 Gm. The valves, the coronary arteries, the myocardium and the endocardium appeared normal. The lungs were congested and edematous. No abnormalities were seen in the liver, and it weighed 1,950 Gm. The kidneys, the right adrenal gland and the pancreas were normal.

A retroperitoneal cyst (fig. 1 *A*), measuring 21 by 17 by 11.5 cm., was found in the left upper quadrant of the abdomen, the outer surface of which was covered by a glistening membrane. The cyst was slightly adherent to the pancreas, the kidney and the spleen by readily broken, thin fibrous strands. The stomach, colon and small intestine were displaced to the right, and the left kidney was displaced downward. The spleen was found to lie anterior to the cyst. The wall of the cyst, in its thinner portions, measured 1 mm. in thickness. The adrenal gland was stretched out over its outer surface in an area measuring 7 by 2 by 0.3 cm., and it could not be detached from the wall. The inner surface of the cyst was smooth except for some slightly elevated flat patches (fig. 1 *B*) of partially calcified orange-brown tissue. The contents of the cyst totaled 2,000 cc. of thin, clear, yellow fluid having a specific gravity of 1.020 and an alkaline p_H. The fluid had a cholesterol value of 33 mg. per hundred cubic centimeters and an albumin-globulin ratio of 2.6:2.4.

Microscopic Observations.—The fibrinous pericarditis was confirmed by microscopic examination. A small patch of bronchopneumonia was found in the lungs. In the spleen, the pancreas and the lymph nodes small arteries showed thickened walls composed of swollen, hyalinized bands of collagen forming an "onion skin" type of lesion. Mononuclear

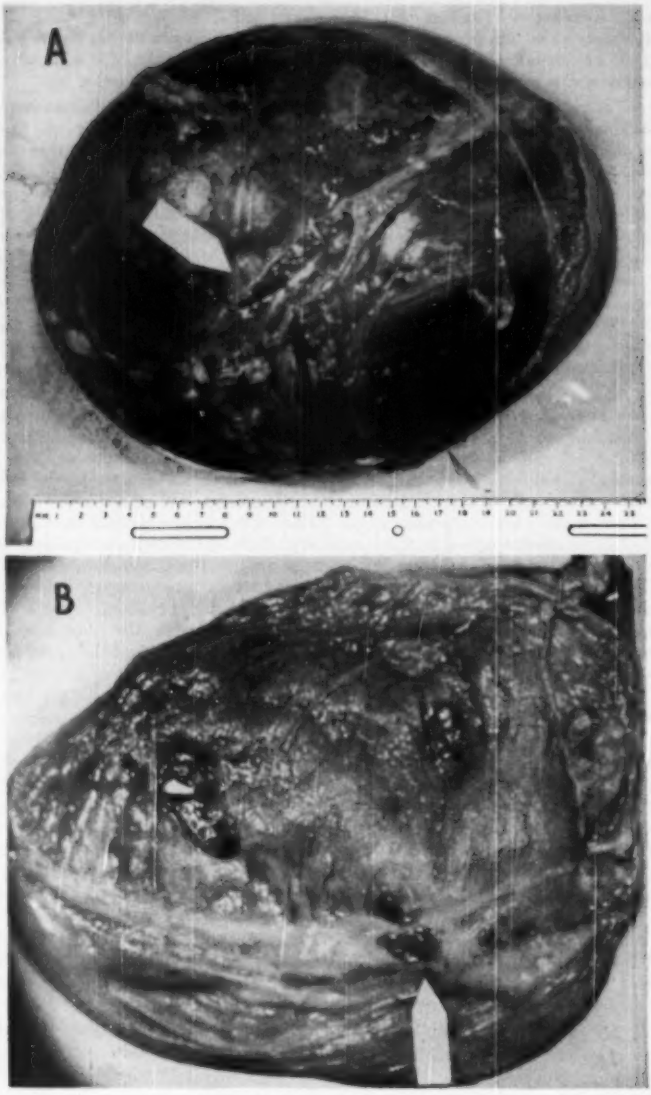

Fig. 1.—*A*, outer surface of the cyst wall. The arrow points to part of the adrenal gland. *B*, the inner surface of the cyst, with the arrow pointing to one of the elevated orange-brown plaques.

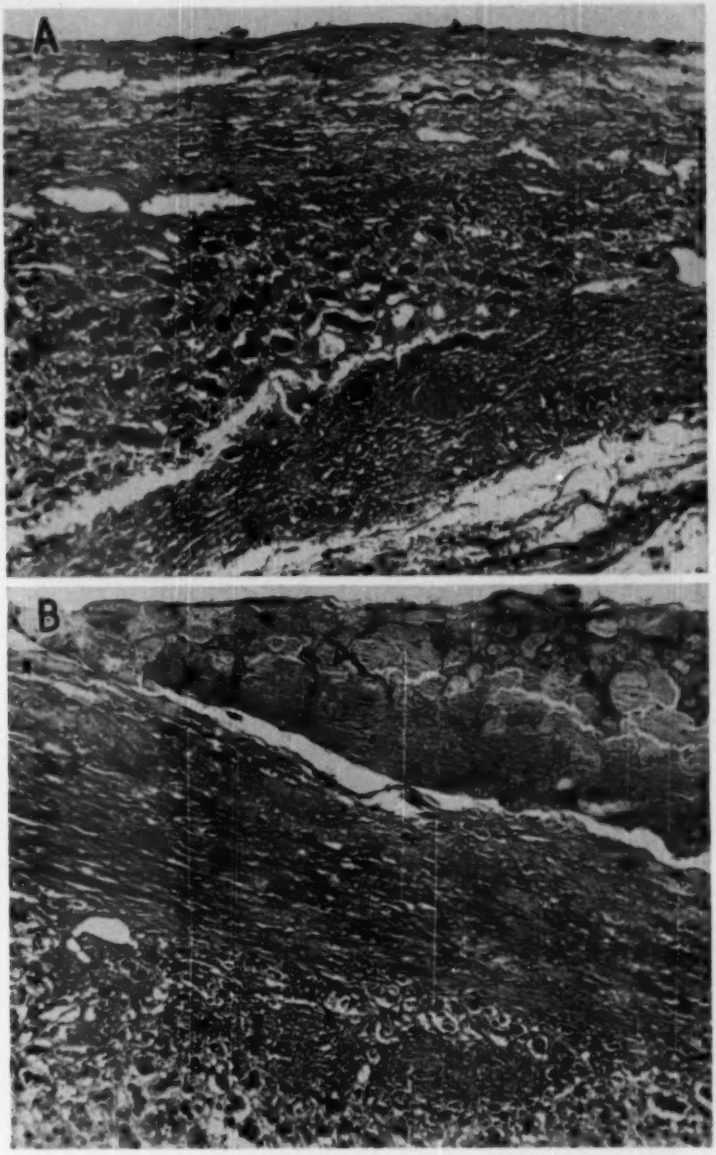

Fig. 2.—*A*, photomicrograph illustrating an island of adrenal cortical cells surrounded by the cyst wall. The inner surface of the cyst is represented by the layer of hyaline tissue in the upper part of the photograph. Hematoxylin and eosin stain; × 100.

B, photomicrograph illustrating a plaquelike collection of fat-laden macrophages on the inner surface of the cyst. Hematoxylin and eosin stain; × 100.

cells had infiltrated the walls of many of these vessels. A few arteries of the pancreas also contained thrombi. The kidneys, the liver and the right adrenal gland were not remarkable.

The adrenal cyst showed small islands of adrenal cortical tissue in various parts of its wall (fig. *2 A*) surrounded on all sides by what appeared to be hyaline tissue with the hematoxylin and eosin stain. This hyalin was elevated in areas along the inner surface of the cyst, simulating hyaline plaques. Also along the inner surface were collections of fat-laden macrophages (fig. *2 B*) resembling atheromatous plaques, and in other areas there were foci of calcification. An elastic tissue stain (fig. 3) showed numerous elastic fibers in the wall. Additional special

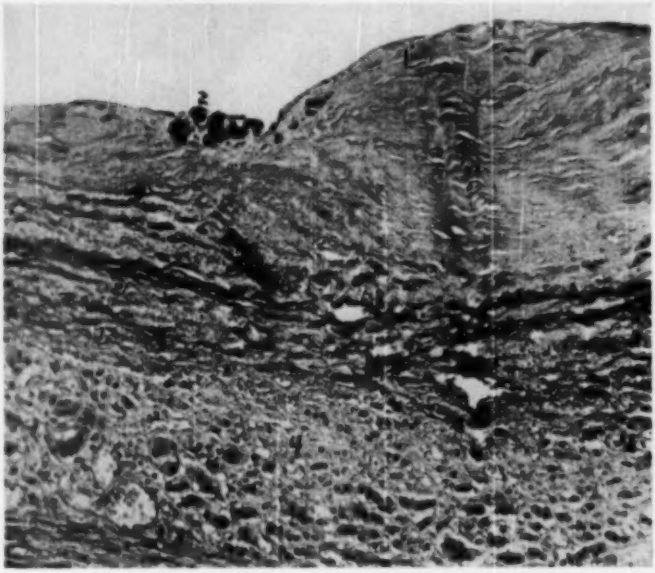

Fig. 3.—This photomicrograph shows a hyaline plaque (*1*), an area of calcification (*2*), bands of elastic tissue (*3*) and an island of adrenal cortical cells (*4*) in the wall of the cyst. The inner surface is represented by the upper margin of the photograph. Verhoeff's elastic tissue stain; × 100.

stains revealed only a few, fine smooth muscle fibers interspersed between the elastic and the hyaline tissue. No definite endothelial lining could be differentiated.

COMMENT

Cyst of the adrenal gland is rare. It has occurred from under the age of 5 up to 70.[1] If large enough, as in the cases noted presently of lymphatic type or pseudocyst, it may be of some importance surgically.

1. Rabson, S. H., and Zimmerman, E. F.: Arch. Path. **26**:869, 1938.

Bourcy and Legueu [2] reported one containing 5 liters of fluid. When the cyst grows, sometimes acutely because of hemorrhage, it may cause pain and other symptoms due to pressure on the surrounding organs or due to the acute process. Roentgenologic studies may be revealing in showing displacement of organs, but a definite diagnosis of a cyst of the adrenal gland probably will not be possible. Other cysts which may be considered in a differential diagnosis are hydatid cyst of the liver or the spleen and cyst of the mesentery, the mesocolon, the pancreas, the spleen or the kidney.

The first instance of cyst of the adrenal gland was reported by Greiselius [3] in 1670. Oberndorfer [4] studied a case of multiple cysts of one adrenal gland. Sick's [5] ciliated epithelial cyst probably resulted from a developmental displacement of tissue of the urogenital anlage. Terrier and Lecène [6] reviewed 9 other cases in addition to their own which were reported up to 1906. They also classified adrenal cyst into five groups:

1. Parasitic cysts. These are rare. Barnett [7] studied 1,617 cases of Echinococcus cyst and found adrenal involvement in less than 0.5 per cent. Similarly, Dew [8] was able to find only a single instance of an adrenal Echinococcus cyst.

2. True glandular or retention cysts. These are extremely rare in man but are frequent in lower animals.[6] They are formed by a cylindric epithelium. There is some doubt as to whether they occur in man because of the poor descriptions given. Also, Stoerk [9] has shown that the adrenal cells do not form true acini with a central lumen out of which a "follicular" cyst could arise as the result of its being distended by the secretion of cells. Cysts of embryonal origin are similar to these and have been referred to by Terrier and Lecène [6] and by Sick.[5]

3. Cystic adenomas. Their size is usually small, and they are more frequent.

4. Serous or lymphangiomatous cysts. Cysts of this nature are much more common. They may attain a very large size and thereby be of surgical interest. The wall is composed of connective tissue, often containing smooth muscle. The cavity is filled with serous fluid and is lined by flattened endothelium.

5. Pseudocysts. Of all, these are the most common. They are caused by hemorrhage or necrosis within normal or diseased parenchyma.

Doran [3] removed a large single cyst surgically and also collected 12 cases from the literature, some of which were mentioned by Terrier and Lecène.[6] De Vecchi,[10] in 1910, reported the first case of bilateral adrenal cyst recorded. He also collected 9 cases, including his own, of cysts of

2. Bourcy, P., and Legueu, F.: J. d'urol. **1**:181, 1912.

3. Greiselius, cited by Doran, A. H. G.: Brit. M. J. **1**:1558, 1908.

4. Oberndorfer, S.: Beitr. z. path. Anat. u. z. allg. Path. **29**:516, 1901.

5. Sick, K.: Virchows Arch. f. path. Anat. **172**:459, 1903.

6. Terrier, F., and Lecène, P.: Rev. de chir., Paris **2**:321, 1906.

7. Barnett, L.: Australian & New Zealand J. Surg. **12**:241, 1942.

8. Dew, H. R.: Hydatid Disease: Its Pathology, Diagnosis and Treatment, Sidney, Australasian Medical Publishing Company, Ltd., 1928, p. 406.

9. Stoerk, O.: Berl. klin. Wchnschr. **45**:773, 1908.

10. de Vecchi, B.: Virchows Arch. f. path. Anat. **200**:151, 1910.

lymphangiomatous origin. Küttner [11] described a large hemorrhagic cyst and reviewed 12 others from the literature. Preusse [12] reported a large cyst associated with amyloid degeneration. In a case of bilateral adrenal cysts described by Major and Black [13] there were coincidental findings of large hemangiomas of the liver and the skull. In more recent years, isolated case reports [14] have appeared. Rabson and Zimmerman [1] reviewed cases of lymph or blood vessel origin.

Certain of these cysts have definitely known etiologic factors; there are a variety of opinions concerning the causes of the remainder. Rarely are they congenital or parasitic. It is believed that some are derived from cystic degeneration of hamartomas [1] or adenomas.[14c] Many are considered cystic dilatations of lymphatic or blood vessels. Origin from hemorrhage and necrosis in normal or diseased adrenal glands may also occur.

In the present case the absence of an endothelial lining does not exclude the possibility of a lymphatic or a blood vessel origin. The presence of a cyst wall containing masses of lipid-laden macrophages, areas of calcification, elastic tissue and a small amount of smooth muscle tend to support a vascular origin. Furthermore, there are other elevated areas along the inner surface resembling hyaline plaques. The finding of calcium,[15] elastic tissue,[16] smooth muscle [17] and sometimes nerve tissue [2] in the walls of cysts has been reported before. However, whether or not an adenoma was present and degenerated is difficult to determine, since it is possible that the lipid in the macrophages was derived from degenerated cortical cells. The coincidental finding of disseminated lupus erythematosus in this case probably bears no relationship to the cyst.

SUMMARY

An instance of cyst of the adrenal gland is reported, with the observations recorded at necropsy. The literature is summarized with reference to the classification of adrenal cysts.

The present specimen revealed elastic tissue, hyaline plaques, calcific deposits and fat-laden macrophages in the wall of the cyst, suggesting a blood vessel origin. The coincidental finding of disseminated lupus erythematosus does not appear to be related.

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11. Küttner, H.: Beitr. z. klin. Chir. Tübing. **82**:291, 1913.

12. Preusse, O.: Zentralbl. f. allg. Path. u. path. Anat. **25**:961, 1914.

13. Major, R. H., and Black, D. R.: Am. J. M. Sc. **156**:469, 1918.

14. (*a*) Ballance, H. A.: Brit. M. J. **1**:926, 1923. (*b*) Levison, P.: Endocrinology **17**:372, 1933. (*c*) Iglitsyn, N. M.: Khirurgiya **1**:115, 1937. (*d*) Reimann, D. L., and Guyton, W. L.: Am. J. Path. **23**:479, 1947. (*e*) Rabson and Zimmerman.[1]

15. Lucksch, F.: Beitr. z. path. Anat. u. z. allg. Path. **62**:204, 1916. Bossard, R.: Ein Fall von Lymphangioma cysticum der rechten Nebenniere, Zurich, Emil Cotti's Wwe., 1900. Riess, P., and Schott, E.: München. med Wchnschr. **76**:621, 1929. Winter, H.: Zentralbl. f. allg. Path. u. path. Anat. **63**:305, 1935. de Vecchi.[10] Major and Black.[13]

16. (*a*) Potherat and Chambord, cited by Brin, M. H.: Assoc. franç. d'urol., Proc.-verb. etc., Par. **15**:33, 1911. (*b*) Oberndorfer.[4] (*c*) Sick.[5] (*d*) de Vecchi.[10]

17. Beck, M.: Zentralbl. f. allg. Path. u. path. Anat. **47**:181, 1929. de Vecchi.[10] Potherat and Chambord.[16a]

General Reviews

PATHOLOGY OF OXYURIASIS

With Special Reference to Granulomas Due to the Presence of Oxyuris Vermicularis (Enterobius Vermicularis) and Its Ova in the Tissues

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IT IS GENERALLY accepted that oxyuriasis (enterobiasis) is the most prevalent of the worm infestations which occur in man, yet descriptions of pathologic changes associated with the presence of threadworms (pinworms) are comparatively uncommon. Moreover, in many cases of Oxyuris infestation, particularly in those in which the intestinal tract is involved, there is reason for questioning the etiologic significance sometimes attributed to the finding of the parasite in diseased areas; the association may well be a fortuitous one, a lesion of independent origin merely providing the parasite with a particularly favorable location in which to continue development or find nourishment, or, at most, facilitating its entry by lessening the vitality of the tissues. It cannot, however, be disputed that the presence of the parasite is the immediate cause of the granulomas which develop around threadworms which have strayed from their usual haunts and died, and around ova deposited in the course of such anomalous wanderings. These granulomas are probably commoner than is recognized. Their presence seldom causes symptoms or complications, and the majority of the recorded examples have been incidental findings at operation or necropsy, most of them in the genital organs or the pelvic peritoneum of women. An account of 3 new cases of Oxyuris granuloma is included in the present report. The first two are typical examples, encountered by chance in the course of gynecologic operations. The third case is that of an adolescent boy who underwent nephrectomy; threadworm ova, surrounded by granulomatous tissue, were present in the kidney and the remains of a mature worm in the ureter. Before describing these cases, a short account of the biology of Oxyuris vermicularis will be given, some recent advances in the epidemiology of oxyuriasis will be summarized, and a review made of the cases previously recorded in which the presence of this parasite has been thought to be intimately related to the pathologic changes occurring in the tissues.

From the Departments of Pathology of the University of Birmingham and of the United Birmingham Hospitals, Birmingham, England.

BIOLOGY OF OXYURIS VERMICULARIS

Oxyuris vermicularis (Enterobius vermicularis) is generally said to be the commonest metazoan endoparasite of man; its distribution is worldwide. It is an obligate parasite, and man is its only natural host; almost all attempts to produce infestation in animals have failed, although other species of Oxyuris are widespread in nature as intestinal parasites of mammals and of some invertebrates. The fully grown female Oxyuris vermicularis is between 8 and 13 mm. long, and 0.6 to 0.8 mm. wide; the male seldom exceeds a length of 2.5 mm., and is slightly more slender than the female. The normal habitat of the mature worm is the lowermost part of the ileum, the cecum, the proximal part of the ascending colon and the vermiform appendix. Copulation occurs here, the male usually being said to die soon afterward. The female then makes her way along the colon to the rectum. If she escapes being expelled during defecation, she passes through the anus to lay her eggs on the adjacent skin, after which she dies. The transanal migration habitually occurs soon after the host goes to bed, the warmth being said to stimulate the worm; however, the same nocturnal periodicity is sometimes observed in infested children who are confined to bed, and warmth is probably not the only factor by which it is determined. Reardon [1] counted the eggs in 20 gravid females and found the mean to be practically 11,000. The average dimensions of the ova are: length, 54 microns; width, 30 microns; thickness, 20 microns. Seen from above when it is lying flat, the ovum is asymmetric, one side being more curved than the other and one end more rounded; if seen, however, along the line of its long axis or of the longer of its transverse axes, it appears as a plump rod-shaped body with rounded ends and measuring 20 microns by, respectively, 30 or 54 microns.[2] Knowledge of the different shapes and measurements of the ova according to the plane in which they are seen is particularly important when they are being identified in histologic preparations. The ovum has a thin, homogeneous, double-contoured shell, within which a very fine membranous lining can sometimes be seen; when laid, the ovum already contains a folded, tadpole-like embryo. The itching caused by the movements of the worm and the presence of ova results in scratching, and ova are transferred on the fingers to the mouth or the nose. Wilhelmi and Quast [3] found Oxyuris ova in dirt beneath the finger nails in just over 60 per cent of 921 school children in Berlin, Germany, and in the nasal mucus in 16 per cent of 25 of them. The ovum is swallowed, and in the stomach and small intestine the shell is softened by the alimentary secretions and the embryo escapes.

1. Reardon, L.: Pub. Health Rep. **53**:978, 1938.

2. Schüffner, W., and Swellengrebel, N. H.: Zentralbl. f. Bakt. (Abt. I) **151**:114, 1943-1944.

3. Wilhelmi, J., and Quast, M.: Klin. Wchnschr. **4**:964, 1925.

After a series of moultings the larva completes its development, becoming the sexually mature parasite, the whole cycle occupying about two weeks. The life of the mature female is said to be from thirty-seven to ninety-three days.[4]

There is no unequivocal evidence that Oxyuris penetrates the intestinal mucous membrane at any stage in its normal life cycle. The larva moves little, and has no cephalic armature; its morphologic appearance suggests that it develops within the lumen of the bowel without migrating into the tissues of the host.[5] Penso,[6] however, after a study of vermiform appendixes of man and of rabbits infested by Oxyuris ambigua, claimed that gravid female worms sometimes enter the mucosa and there lay eggs, which may hatch in the tissues and later reestablish intestinal infestation. Smalt[7] was unable to find evidence, either in a mouse fed with ripe ova of O. vermicularis or in man, of a developmental stage of Oxyuris which is passed in the host's tissues, and he refers to similar lack of success of Japanese workers investigating animals artificially infected with this parasite.

OXYURIASIS

Epidemiology and Diagnosis.—The incidence of oxyuriasis varies in different places. It is highest in backward communities and among the poor. Infestation is commoner in children and is particularly prevalent in children's institutions. It occurs more frequently in the female, both child and adult.[8] In assessing figures of the incidence of oxyuriasis, account must be taken of the method of investigation which has been used. Examining feces for the presence of the parasite is valueless, as ova are seldom found in the stool, and mature worms, of which only females are easily visible to the unaided eye, readily escape observation and may be scanty. Flotation and decantation or concentration methods of fecal examination are too time-consuming to be of general use, although essential to accurate investigation of the incidence of oxyuriasis at necropsy. Satisfactory for clinical and most epidemiologic purposes are various modifications of the methods designed to detect the characteristic ova on the perianal skin, the usual site of oviposition. Of these, the method which has been most widely used is that of Hall,[9] the National Institute of Health swab (NIH swab).

4. Schüffner, W.: Zentralbl. f. Bakt. (Abt. 1) **152**:67, 1947.

5. Brumpt, E.: Précis de parasitologie, ed. 6, Paris, Masson & Cie, 1949, pp. 850-861.

6. Penso, G.: Ann. de parasitol. **10**:271, 1932.

7. Smalt, F. H.: Nederl. tijdschr. v. geneesk. **90**:333, 1946.

8. Fischer, W.: Die tierischen Parasiten des Darmes, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Springer-Vorlag, 1929, vol. 4, pt. 3, pp. 697-702. Brumpt.[5]

9. Hall, M. C.: Am. J. Trop. Med. **17**:445, 1937.

Even with this swab, the percentage of positive results increases with the number of investigations carried out on each person; e. g., Sawitz, Odom and Lincicome [10] showed that one NIH swab per person revealed 72 per cent of the total number of persons with threadworm infestation, while 87 per cent were revealed when the examination was repeated three times on alternate days, 92 per cent when it was repeated five times and 96.2 per cent when repeated seven times. Schüffner and Swellengrebel [11] described a procedure which has proved to be more rapid and more convenient than the use of the NIH swab, and which, they say, is at least three times as reliable.

Manner and Source of Infection.—Schüffner [12] described four distinct types of Oxyuris infection. The commonest type, type D (digital infection), is maintained by the transferring of ova from the patient's anus to his mouth (or nose) on his fingers. It is the usual type in children; among adults it occurs only in the uncleanly or in those living under poor conditions, and in patients with mental disease. This type of infestation is heavy and continuous; large numbers of ova are present in perianal preparations. Type C ("contact" infection) is the result of a single intake of ova in food contaminated from another source through the medium of fingers, flies or dust; its onset is sudden, and the severity depends on the number of viable ova ingested and the reaction of the patient. In the absence of complicating factors, e. g., digital reinfection, this type dies out spontaneously within a few days or weeks. Type S infection (dust infection—*Staub-Infektion*) is characterized by long periods of freedom, when the patient is away from the contaminated environment, e. g., during school vacations, and by relatively light infestation and the finding of only a small number of ova. Cram [13] found ova in the dust of all rooms in the houses of seven families with infested members, contamination being heaviest in bedrooms; threadworm ova have often been found in bedding, and Lentze [14] showed that microscopic threadlets of fabric could carry them in the air; Schüffner and Swellengrebel [2] found ova numerous in the dust of schoolrooms, water closets and a school dining room. Schüffner [4] proved the infectivity of such ova, the youngest of which were known to be at least 4 days old. He also mentioned that when an egg which had been stored dry for eight weeks was placed in a suitable medium the embryo

10. Sawitz, W.; Odom, V. L., and Lincicome, D. R.: Pub. Health Rep. **54**:1148, 1939.

11. Schüffner, W., and Swellengrebel, N. H.: Zentralbl. f. Bakt. (Abt. 1) **151**:71, 1943-1944. Leading Article: Threadworms, Lancet, **1**:742, 1946. Schüffner, W.: Lancet **1**:872, 1946.

12. Schüffner, W.: Zentralbl. f. Bakt. (Abt. 1) **154**:220, 1949.

13. Cram, E. B.: Am. J. Dis. Child. **65**:46, 1943.

14. Lentze, F.-A.: Zentralbl. f. Bakt. (Abt. 1) **135**:156, 1935-1936.

was seen to hatch. When kept moist, however, the ovum dies within a few days. The fourth type of infection which Schüffner [12] described is of particular interest because it explains the persistence of infestation in some patients whose personal hygiene is above reproach and who are not exposed to other hazards of reinfection. This type, type R, he names "retrofection." It is due to larvae which hatch in the anal region and pass in through the anus, giving rise to a recurrence of the intestinal infestation. These recurrences may occur with a definite five to seven weeks rhythm. In "retrofections," so far recognized only in adults, the periods during which ova cannot be found at the anus never exceed the life span of the female worm, as the infestation dies out when the females are no longer present to give rise to new generations of ova and so to further retrograde infection.

Prevalence.—Some recent figures of the incidence of oxyuriasis are: Boston, Mass., 19 per cent of 505 white children in the Children's Hospital [15]; Washington, D. C., 41.5 per cent of 2,895 white people and 12.9 per cent of 1,099 Negroes, the sampling being described as representing a fair cross section of the population [15]; Toronto, Canada, 60 per cent of 300 children and 52 per cent of 56 adults living at home [16]; Munich, Germany, 71.4 per cent of 182 children attending a polyclinic.[17] Cram [18] recorded that Oxyuris ova were found in 43 per cent of over 22,000 people in the United States of America (including Puerto Rico), Canada, the Philippines and four European countries. The incidence of oxyuriasis in Britain does not appear to have been the subject of any large scale studies. Young's [19] figures refer only to two small groups of children, one a series of 119 patients in a children's hospital near London, England, and the other a group of 40 children in a residential nursery school in London; she found 42 per cent of the former and 55 per cent of the latter infested. NIH swabs or other reliable methods of examination were used in all of the aforementioned investigations.

Symptoms.—Symptoms which can be directly attributed to oxyuriasis are practically limited to the irritation of the skin caused by the nocturnal wanderings of the gravid female worms and the complications which may follow the resulting scratching, particularly the eczematous dermatitis of the perianal, natal and vulval or scrotal skin, which may spread to the thighs and abdominal wall and become the site of secondary bacterial infections. Intestinal symptoms are uncommon, but heavy

15. Weller, T. H., and Sorenson, C. W.: New England J. Med. **224**:143, 1941.
16. Kuitunen-Ekbaum, E.: Canad. M. A. J. **48**:229, 1943.
17. Mendheim, H., and Scheid, G.: Med. Monatsschr. **2**:147, 1948.
18. Cram, E. B., in Christie, J. R.: An Introduction to Nematology, Babylon, N. Y., 1941, sec. 2, pt. 2, p. 323.
19. Young, M. R.: Proc. Roy. Soc. Med. **35**:684, 1941-1942.

infestation may be associated with diarrhea and excessive mucus in the stools, which may even be slightly streaked with blood. The relationship between oxyuriasis and enuresis, masturbation, urticaria, "fits," "neurasthenia" and the like is usually equivocal.

It must be remembered that in a considerable proportion of those harboring threadworms symptoms are insignificant or absent.

Presence of Oxyuris in Atypical Sites.—Oxyuris is seldom found elsewhere than in the contents of the intestine or on the skin in the immediate vicinity of the anus. Away from these sites its ova occur on the fingers and, less commonly, on the skin of other parts and in nasal secretion.[5] Very rarely, larvae [20] or mature worms [21] have been seen in the nose or the mouth.[22] They are said to have been found in the esophagus and the stomach.[5]

The gravid female may migrate from the anus over the perineum and into other orifices in the region. I have seen a gravid oxyurid and Oxyuris ova in the subpreputial exudate in a 4 year old child with phimosis complicated by suppurative balanoposthitis. Max Koch [23] mentioned that Oxyuris can enter the urinary bladder through fistulas communicating with the bowel or, in the female, *per urethram*. Oxyuris ova are sometimes found in the urine,[24] but usually only after this has become contaminated from ova laid on the vulva or adhering to the penis after natural or unnatural intercourse. Chiari [25] stated that it is well known to urologists that the clinical signs of cystitis often develop in small girls suffering from oxyuriasis and that the cystitis subsides on specific treatment of the infestation. I have failed to find in the literature any statement indicating that threadworms or their ova had been seen in the ureter or the kidney, and case 3 of the present paper appears, therefore, to be unique.

Oxyuris may enter the vagina and wander through the female genital tract. Vaughan [26] described a case of severe vulvovaginitis due to this parasite in a girl aged 6 years. Spitzer [27] examined a 12 year old

20. Proskauer, T.: Ztschr. f. Ohrenh. **21**:310, 1891.

21. Chiari, O.: Erfahrungen auf dem Gebiete der Hals- und Nasen-Krankheiten nach den Ergebnissen des Ambulatoriums, Leipzig and Vienna, Toeplitz & Deuticke, 1887, p. 81. Hartmann, A.: Berl. klin. Wchnschr. **26**:78, 1889.

22. Pomper, A.: Ein Beitrag zur Lehre vom Oxyuris vermicularis, Berlin, A. Hirschwald, 1877.

23. Koch, M.: Die tierischen Schmarotzer des Harnapparates, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Springer-Verlag, 1925, vol. 6, pt. 1, p. 752.

24. Kouri, P.; Arenas, R., and Basnuevo, J. G.: Vida nueva **33**:114, 1934. Koch.[23]

25. Chiari, H.: Virchows Arch. f. path. Anat. **269**:730, 1928.

26. Vaughan, R. A.: St. Louis Clin. Rec. **7**:271, 1880-1881.

27. Spitzer, B. B. R.: Wien. med. Wchnschr. **42**:6, 1892.

child who had a profuse vaginal discharge which led her parents to suspect that she had been seduced and had contracted gonorrhea. He found the vulva to be eczematous, and there was a slimy, purulent vaginal discharge; the hymen admitted only a glass catheter. Irrigation of the vagina produced a knot of threadworms, and a santonin enema completed the cure. Heller [28] found an oxyurid in the vaginal vault. Simons [29] was consulted by a multipara aged 42, who for six months had noticed a slight bloody discharge from the vagina. He was struck by the peculiar aromatic odor of the discharge. Through a speculum he saw on the portio a worm, 1.5 cm. long, "probably a female oxyuris," which disappeared into the cervix, which was eroded; when, after a minute's delay, he scooped out the cervical canal, he found a second, smaller worm. Four weeks later there was no abnormality. The patient gave a long history of anal itching and had an old second degree perineal tear. Vix [30] found embryo-containing threadworm ova in uterine secretion obtained after passing a sound under direct vision. Leuckart [31] noted skeptically that Benedetti had claimed to have found threadworms between the placenta and the uterine wall; it has proved impossible to trace Benedetti's original account of this observation, the source of which was not given by Leuckart or by the many subsequent authors who have referred to it. Tschamer [32] reported the chance finding of two live female threadworms in an otherwise normal fallopian tube removed from a 31 year old woman in the course of a radical operation for choriocarcinoma. Examination of this woman's feces disclosed no evidence of infestation, but she gave a history of "worms" and anal itching.

This series of reports is of interest, indicating the progressively deeper incursion of worms within the lumen of the female genital tract. While there may be doubt as to the exact identity of the parasite in some of these cases, more exact studies have been made in cases in which the parasites had produced actual lesions at various sites in the genitalia (see later section). There can no longer be any question that O. vermicularis occasionally passes from the vulva to the peritoneal cavity within the lumen of the female reproductive tract.

Threadworms have only once been reported in the peritoneal cavity of the male in the absence of a perforation of the intestinal wall.

28. Heller, A.: Deutsches Arch. f. klin. Med. **77**:21, 1903.

29. Simons, E. M.: Centralbl. f. Gynäk. **23**:777, 1899.

30. Vix, E.: Ueber Entozoën bei Geisteskranken, insbesondere über die Bedeutung, das Vorkommen und die Behandlung von Oxyuris vermicularis, Berlin, A. Hirschwald, 1860.

31. Leuckart, R.: Die menschlichen Parasiten und die von ihnen herrührenden Krankheiten, Leipzig and Heidelberg, C. F. Winter, 1876, vol. 2, p. 345.

32. Tschamer, F.: Zentralbl. f. Gynäk. **43**:989, 1919.

Susman [33] saw six threadworms "actively crawling on the peritoneal surface of the caecum" of a boy aged 8 years, who had had symptoms of acute appendicitis ten days previously. The tip of the appendix was inflamed, with omentum wrapped around it, but no perforation could be found in it or in the cecum or the ileum. Appendicectomy was performed, but whether the worms were seen before this or only afterward is not stated; no worms were found in the appendix when it was opened.

PATHOGENICITY OF OXYURIS VERMICULARIS

Oxyuriasis is seldom associated with pathologic changes which can be directly attributed to the presence of the parasite. Of first importance in this respect is consideration of the question whether Oxyuris can penetrate into normal tissues. It has already been mentioned that there is no unequivocal evidence of a developmental stage passed within the tissues. Undoubtedly, the larvae of Oxyuris, in contrast with those of Ascaris lumbricoides, do not enter the blood stream, and there is no justification for the statement made by French [34] that pulmonary and cerebral localization of the parasite accounts for the cough, hemoptysis and convulsions which he said may be associated with oxyuriasis. Many authors, e. g., Askanazy [35] and Fischer,[6] although it is not clear on what evidence, have stated that the mature worm may either live free in the intestinal lumen or attach itself to the mucosa. In the first case its nourishment is obtained from the feces; in the second it burrows forward for a short distance into the tissues to feed on the tissue juices, never penetrating, however, to a depth greater than two thirds of its own length. Some authors [36] have stated that the mature worm is normally attached to the mucosa. Fixation to the mucous membrane explains those cases in which worms have been scanty or absent in the stools, yet are found in large numbers in the intestinal contents post mortem; soon after death of the host they are said usually to detach themselves from the bowel wall. Penetration of the surface of the mucosa is said to produce petechial hemorrhages, observed first by Froelich [37] in the rectum. That the parasite does sometimes wander deeply into living tissues is shown by the occasional finding of dead

33. Susman, M. P.: J. Coll. Surg. Australasia **2**:273, 1929-1930.

34. French, H., in French, H., and Douthwaite, A. H.: An Index of Differential Diagnosis of Main Symptoms, ed. 6, Bristol, John Wright & Sons Ltd., 1945, p. 200.

35. Askanazy, M., in Aschoff, L.: Pathologische Anatomie, ed. 6, Jena, Gustav Fischer, 1923, pp. 282-284.

36. Belding, D. L.: Textbook of Clinical Parasitology, New York, Appleton-Century-Crofts, Inc., 1942, p. 308. Faust, E. C.: Human Helminthology, ed. 3, London, Henry Kimpton, 1949, p. 460.

37. Froelich, R.: Rev. mens. d. mal. de l'enf. **15**:497, 1897.

worms or deposits of ova, surrounded by necrotic or granulomatous tissue and a fibrous capsule. Ruffer [38] was the first to describe such lesions. At necropsy on an Egyptian workman, aged about 35 years, who had died of a "chronic cirrhotic disease" of liver and kidneys, he found a number of firm nodules in the wall of the large bowel. Their size varied from that of a pinhead to that of a "small nut." Accustomed to finding bilharzial nodules in 50 per cent of necropsies in Egypt, Ruffer thought that the lesions in this case were of the same nature. However, each nodule examined proved to be a calcified mass, surrounded by connective tissue and containing innumerable typical Oxyuris ova, some of which were studded with crystals that dissolved in mineral acid, liberating gas. No worms were found in the lesions. In the smaller "calculi" many ova contained embryos. Wagener [39] found hemispheric grayish nodules, not larger than a pinhead, in Peyer's patches in the lower part of the ileum in 11 necropsies, most of these on children between 3 and 10 years old. Up to 20 nodules were discovered in the younger subjects; only one or two, in the older. Identifiable remains of a very young oxyurid, calcified and surrounded by cellular detritus, were present in some of the nodules. Similar findings were reported by other authors.[40] The presence of threadworms wholly buried within the tissues may be explained as due either to abnormally deep (complete) penetration of the living mucosa and subsequent onward burrowing or [41] to death of the tissue encouraging farther penetration.

The published reports of visceral lesions caused by Oxyuris, or of which this parasite was the suggested cause, can be reviewed under a number of headings.

Oxyuris and Appendicitis.—Rochaz,[42] in a study of appendical "calculi," mentioned that worms (Trichuris?) were observed in the appendix and described by Santorini as early as 1724; he himself observed ova of Ascaris and of Oxyuris in fecal masses from the appendix but expressed the belief that worms did not occur in that organ during life. Still [43] drew attention to the frequent presence of threadworms in this site. Girard [44] found two whipworms in a child's appendix; one had partially buried itself in the mucosa, and the only

38. Ruffer, M. A.: Brit. M. J. **1**:208, 1901.

39. Wagener, O.: (*a*) Deutsches Arch. f. klin. Med. **81**:328, 1904; (*b*) Virchows Arch. f. path. Anat. **182**:145, 1905.

40. (*a*) Edens: Centralbl. f. Bakt. (Orig.) **40**:499, 1906. (*b*) Zinn, W.: Therap. Monatsh. **24**:1, 1910.

41. Gordon, H.: Arch. Path. **16**:177, 1933.

42. Rochaz, G.: Rev. méd. de la Suisse Rom. **14**:637, 1894.

43. Still, G. F.: Brit. M. J. **1**:898, 1899.

44. Girard, J.: Ann. Inst. Pasteur **15**:440, 1901.

inflammatory changes were at this site. On the basis of these and similar reports, and in the belief that he had observed cure of appendicitis in worm-infested patients treated with anthelmintics, Metchnikoff [45] formed the opinion that nematodes were the cause of a large number of cases of appendicitis. The relationship of helminthiasis, particularly oxyuriasis, and appendicitis has been the subject of much discussion since then. The long controversy over this aspect of oxyuriasis is now mainly of historical interest,[46] and the view of Aschoff and his school is the one most widely accepted, although some French parasitologists, e. g., Brumpt,[5] follow Metchnikoff's teaching and still consider that Oxyuris is an important factor in the genesis of appendicitis. As Aschoff [47] stressed, threadworms in the appendix may cause "appendical colic" or symptoms resembling those of true appendicitis (Hueck's [48] "appendicopathia oxyurica" [49]); examination of the organ in such cases shows no abnormality other than the presence of the parasite in the lumen, and, at most, small mucosal petechiae identical with those, possibly the result of surgical trauma, which are often seen in appendixes free from worms. Aschoff's belief that Oxyuris does not cause true appendicitis is fully justified in the case of the common and most dangerous variety of that disease, that in which gangrene and perforation rapidly develop. Hueck [48] found no evidence that Oxyuris is a significant cause of appendicitis, either in a series of appendixes personally studied or in a critical review of the literature. Gordon [41] reached the same conclusion after reviewing the literature and on the basis of his examination of just over 26,000 consecutive appendicectomy specimens. He found Oxyuris in 311 cases (1.19 per cent). Small mucosal lesions (punctate hemorrhage, slight exudation, small areas of necrosis) were present in 12 of these. In 33 cases the worm was found in the wall of the appendix, but there was no sign that the organ had reacted to its presence, which Gordon believed to be the result of invasion of the tissue subsequent to operation. He found no case in which the worm appeared to have invaded living tissues, as shown by any vital reaction on the part of the latter, but in 1 case in which

45. Metchnikoff, E.: (*a*) Rev. gén. de clin. et de thérap. **15**:185, 1901; (*b*) Bull. Acad. de méd., Paris **45**:301, 1901.

46. For the literature see E. Christeller and E. Mayer, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Springer-Verlag, 1929, vol. 4, pt. 3, pp. 560-569.

47. Aschoff, L.: Med. Klin. **91**:249, 1913.

48. Hueck, O.: Frankfurt. Ztschr. f. Path. **13**:434, 1913.

49. The term "appendicopathia oxyurica," usually attributed to Aschoff, appears to have been originated by Hueck,[48] working in Aschoff's institute. The latter used the expression in a paper [47] prepared and published while Hueck's work [48] was still in the press.

Oxyuris was present in the lumen a granuloma was present around a calcified mass in the appendical wall, which he suggested might have been a dead parasite.

I have found in the literature no convincing account of an Oxyuris granuloma of the appendix. However, granulomatous reaction associated with the presence of Oxyuris in this organ, with multinucleated giant cells, tissue eosinophilia and necrosis, is mentioned in a few textbooks, e. g., by Askanazy [48] and by Schenken and Burns,[50] but in no case is the source of the information quoted or an illustration given. Observations already referred to [51] showed that Oxyuris can cause intramural intestinal lesions; this being so, it is surprising that similar lesions of the appendix have not attracted more attention, for they may certainly be expected to occur. If, entering the tissues, the worm carries with it pathogenic bacteria, the latter might indeed set up true appendicitis; such an occurrence, however, must be rare.

Intestinal Lesions and Oxyuriasis.—The intestinal lesions undoubtedly caused by Oxyuris have been few [51] and without serious significance. The role of Oxyuris in the development of intestinal ulcers in association with which it has been found is less clear. Läwen and Reinhardt,[52] reporting the necropsy of a 75 year old man, stated that there were multiple small ulcers in the colon; thousands of threadworms were present and were particularly numerous in the ulcers. Somewhat similar cases have been described by Nathorff [53] and Bijlmer.[54] In Bijlmer's case, tens of thousands of threadworm larvae were present in the wall of the bowel, particularly in that of the rectum, but also throughout the colon and in the ileum. He suggested that the worm invasion probably occurred before death but was secondary to a preexisting ulcerative enterocolitis. These cases suggest that a similar ulcerative enterocolitis may have been present in the unusual case reported by Rodenwaldt and Röckemann,[55] whose patient, a woman of 21, had had intractable diarrhea since the age of 15 years. They found innumerable Oxyuris larvae in the thin, mucous stools but no adult parasites; no pathologic examination was possible, and the case was recorded because it was thought to indicate the possibility of Oxyuris passing its entire developmental cycle within the large bowel, without peroral reinfection.

50. Schenken, J. R., and Burns, E. L., in Anderson, W. A. D.: Pathology, London, Henry Kimpton, 1948, p. 845.

51. Ruffer.[38] Wagener.[39] Edens.[40a] Zinn.[40b]

52. Läwen, A., and Reinhardt, A.: München. med. Wchnschr. **66**:1433, 1919.

53. Nathorff: Neue deutsche Klinik (supp. 3) **13**:48, 1935; quoted by Melchior: Zentralbl. f. Chir. **63**:379, 1936.

54. Bijlmer, J.: J. Parasitol. **32**:359, 1946.

55. Rodenwaldt, E., and Röckemann, W.: Zentralbl. f. Bakt. (Abt. 1) **86**:421, 1921.

Hueter [56] studied material from the case of a middle-aged woman with a history of intestinal hemorrhage; a firm infiltration was found in the rectal wall above the anal sphincter, diagnosed clinically as carcinomatous, and excised. Histologically, venous varices and mucosal ulceration were found, with prominent collections of eosinophil granulocytes; Oxyuris ova, of which he gives a convincing photomicrograph, were present in the granulation tissue; there was no neoplastic condition. Originally, Hueter [56a] misinterpreted the ova as coccidia, and the acid-fast Charcot-Leyden crystals as their merozoite stage, and the case was published as one of intestinal coccidiosis of man; in the amending report [56b] he suggested that the ova had probably been deposited on the floor of a hemorrhoidal ulcer.

Dmitrieff [57] operated on a 44 year old man with a seven day history of intestinal obstruction; ulceration of the cecum was found, with a minute perforation through which an oxyurid escaped into the peritoneal cavity. Recovery followed resection of the ulcerated area, which is said to have shown no unusual pathologic features. Oxyuris ova were present in the stools. In a case reported by Stokes [58] there was actual mechanical obstruction of the splenic flexure by threadworms.

Alfejew [59] reported finding Oxyuris deep within a large histologically benign leiomyoma of the ileum, discovered at necropsy on a woman of 60 who had died of peritonitis due to perforation of the affected bowel. There was a slight inflammatory reaction around the worm, which the author presumed had penetrated into the tumor through the deeply ulcerated surface. Elsewhere in the tumor she found a calcified structure which she described as probably A. lumbricoides. Dead ascarids had been found at necropsy in the abdominal cavity. While the identity of the calcified parasite may be in doubt, the drawing of the oxyurid in the tumor is quite characteristic.

Anschütz [60] studied 2 cases of cecocecal invagination due to local typhlitis associated with nematodal penetration of the mucosa; eosinophil granulocytes were very numerous in the inflamed tissues. The patients were men aged 38 and 24. In the first the parasite was Trichocephalus dispar (Trichuris trichiura); in the second, O. vermicularis.

Schmidt [61] and Fischer [62] reported a case of fistula leading from the ascending colon to the site of a 5 year old shell-splinter scar below

56. Hueter, C.: (*a*) Zentralbl. f. allg. Path. u. path. Anat. **30**:675, 1919-1920; (*b*) **31**:432, 1920-1921.
57. Dmitrieff, J. P.: Zentralbl. f. Chir. **53**:1876, 1926.
58. Stokes, A. C.: Nebraska M. J. **14**:83, 1929.
59. Alfejew, S.: Ztschr. f. Parasitenk. **1**:423, 1928-1929.
60. Anschütz: Klin. Wchnschr. **1**:2174, 1922.
61. Schmidt, W. T.: München. med. Wchnschr. **70**:495, 1923.
62. Fischer, W.: Klin. Wchnschr. **2**:642, 1923.

the umbilicus. The patient said that there had been no injury to the bowel at the time of the war wound, and stated also that he had never had worms until about one year before the fistula developed. Mucus and numerous threadworms were discharged through the fistula, especially in the evenings. Six weeks after it appeared the fistula was excised. There was a heavy eosinophil cell infiltration of the tissues around the fistula, and in one place, immediately beneath the skin, Oxyuris ova were found in the inflamed tissue; the foreign body giant cells around the ova indicated that the presence of the latter was not to be explained as an artefact. Each author suggested that the fistula was the direct result of oxyuriasis, and the history of an old wound quite coincidental. This does not seem probable.

In none of the cases reviewed is there a clear causal relationship between the infestation and the intestinal lesion. The same is true of the 4 recorded cases [63] of intestinal ulceration in apes infested with threadworms (Oxyuris anthropopitheci).

Oxyuris in Lesions of the Anorectal Region.—In all but one of the seven reported cases of anorectal lesions containing Oxyuris the patients were male. The exception [64] was a 50 year old woman with a tumor in the rectovaginal septum which extended into the anterior wall of the rectum; it was not ulcerated. The mass was excised and found to consist of chronically inflamed connective tissue, throughout which were numerous epithelial structures; the latter were composed of atypical stratified squamous epithelium, with a few areas of tall columnar epithelium. What seems to have been a gravid oxyurid was found inside one of the epithelial complexes near the center of the tumor, which probably originated in a remnant of Gartner's duct. How the worm reached this site was not clear.

The case described by Froelich [37] and Vuillemin [65] was that of a boy aged 11 years who had had intestinal oxyuriasis for several months. In the course of eight days, a small, superficial perineal tumor developed, 3 cm. in front of the anus; incision released pus containing more than 60 live threadworms, all those examined (30) being females; there is no note whether the worms were gravid or whether ova were present in the pus. The skin was intact, and no communication could be found between the rectum and the abscess cavity, which were separated by tissue more than 2 cm. thick. There were, however, scattered petechiae in the rectal mucosa, at the center of some of which shallow ulcers were seen which could be probed to a depth of up to 2 mm.

63. Weinberg, M.: Ann. Inst. Pasteur **21**:417, 1907. Troisier, J., and Deschiens, R.: Ann. de parasitol. **8**:562, 1930.

64. Kecht, B.: Wien. med. Wchnschr. **83**:581, 1933.

65. Vuillemin, P.: Centralbl. f. Bakt. (Orig.) **32**:358, 1902

Weigmann [66] and Anschütz [67] reported a similar occurrence in a boy of 6 years with long-standing oxyuriasis. He was admitted with bilateral perianal abscesses of a few days' duration; pus obtained on incision contained live female threadworms. Histologic examination of some excised tissue showed granulation tissue surrounding gravid females and free ova. The skin was intact in this case, also, and again no communication could be demonstrated between the abscesses and the bowel. Anschütz [67] explained these 2 cases and a further case of his own, of which he gives no details, as due to direct Oxyuris penetration of the rectal wall, the parasite accompanied by bacteria which caused the suppuration. As Unterberger [67] said, however, it would be possible to overlook a small fistula in the rectal wall through which a worm might easily pass. Nathan [68] described 2 similar perianal lesions: The first, in a young man, presented as an "abscess" which did not soften when poulticed and was therefore excised, numerous Oxyuris ova being found in sections of the granulomatous tissue. The second was a chronic perianal abscess from which, the patient said, worms had been discharged, his description tallying with that of Oxyuris; Nathan could find no worms or ova in the specimen, which consisted of granulation tissue rich in eosinophil granulocytes.

Fitzwilliams [69] presented a case of recurrent perianal abscess with a twenty-one month history. The patient, a youth aged 17, had had threadworms since childhood. The diseased tissue was excised, neither fistulas nor sinuses being found. Histologic examination showed eggs, thought at first to be bilharzial but later correctly identified as Oxyuris ova. "Worms" were present in the stools. Marshall and Wood [70] found many live threadworms and ova in the thin gray fluid obtained on incision of a recurrent ischioanal abscess in a boy aged 10 years. They suggested that the worms or their ova gain access to the tissues through the crypts of Morgagni.

It can be said that in none of these cases is there proof either of the route by which the parasite reached the site of the lesion or of its having caused the lesion. Penetration of the intact rectal or anal lining is not to be excluded, but an alternative which is at least equally reasonable seems to be suggested by the easy passage offered to the parasites by the small breaches in surface continuity which result from the repeated minor traumas to which the area is subjected. In such a case as that of Fitzwilliams [69] it would not be surprising that worms in their nightly

66. Weigmann, F.: Berlin. klin. Wchnschr. **58**:732, 1921.
67. Unterberger, F.: Centralbl. f. Bakt. (Orig.) **47**:495, 1908.
68. Nathan, H.: Frankfurt. Ztschr. f. Path. **36**:82, 1928.
69. Fitzwilliams, D. C. L.: Proc. Roy. Soc. Med. **27**:932, 1934.
70. Marshall, G. R., and Wood, Q. L.: Northwest Med. **37**:180, 1938.

wanderings should chance along the ready-made pathway of the sinus from a discharging abscess cavity.

Some Miscellaneous Lesions Containing Oxyuris.—Nathan,[68] at necropsy of a 40 year old woman who had died of Laennec's cirrhosis, found a firm whitish nodule, "about as large as a cherry," in the middle of the spleen. Sections showed a gravid oxyurid, surrounded by cellular exudate including eosinophil granulocytes and foreign body giant cells. Elastin-staining suggested that the granuloma had developed in a vein. The author considered that the worm, having somehow entered the portal blood stream, had been carried into the spleen by reason of the circulatory disturbance associated with the hepatic disease.

At laparotomy on a 38 year old woman with a 2 year history of biliary colic, Dieckmann [71] found 6 yellowish nodules in the liver, each about 2 cm. in diameter and containing "ascarides and oxyures." The parasites are not described, and there must obviously be doubt as to their identity. At a second operation on this patient, two years later, ascarids were removed from the extrahepatic bile ducts and from the duodenum and jejunum.

Melchior [72] introduced a new conception of the significance of the presence of Oxyuris in diseased tissues, based on his observations in the case of a boy of 10 years. The child had undergone an operation for uncomplicated bilateral inguinal hernias; the postoperative course was normal, the sutures were removed on the ninth day, and the child was discharged as cured three days later. He was readmitted after six weeks, as a small area in the scar on the left side had broken down, discharging "feces." A typical stitch sinus, into which a probe entered only to a short depth, was found, and some days later a silk suture was removed from it. The lesion healed, and the boy was discharged after three and a half weeks in hospital. Five weeks later he was again admitted with a small sinus; this was explored with a fine crochet hook, and a live oxyurid extracted; several more worms of the same species were found. Healing was rapid. Threadworms were present in the stools, and for this he was successfully treated. In view of the alleged fecal discharge Melchior investigated the possibility that there was a fistulous communication between the bowel and the herniorrhaphy wound, although the normal healing of the original incision seemed inconsistent with the presence of a fecal fistula; no fistula could be demonstrated, and no carbon appeared in the exudate from the sinus after charcoal had been given by mouth. He suggested that worms, aided by the surgical dressings and the moisture of the skin, found their way from the anus to the sinus, or, alternatively, that the patient

71. Dieckmann, A.: Beitr. z. klin. Chir. **131**:373, 1924.

72. Melchior, E.: Zentralbl. f. Chir. **63**:379, 1936.

contaminated the wound with ova carried on his fingers. He discussed the environmental conditions essential to the maturing of an ovum to an adult parasite (ferments to digest the shell, anaerobiosis) and believed that they would prevail in a wound. He therefore suggested the possibility of what he called a true wound parasitism, i. e., development of threadworms *ex ovo* in the granulating tissue, comparable with the development of fly maggots in such tissue, and not of pathogenetic significance (in contrast with the inflammatory reaction associated with dermal myiasis [73]). That mature worms migrated directly into the stitch sinus seems the more probable explanation.

Oxyuris in Lesions of the Female Reproductive System and of the Peritoneum.—For purposes of review it is convenient to group the published cases of oxyuris-containing lesions of the female genitalia with those of the peritoneum, as without exception all the peritoneal lesions have been found in women, the majority in the pelvis, and the parasite appears to gain access to the peritoneal cavity through the genital tract.

(*a*) Intrinsic Genital Lesions: Klee [74] was the first to report finding Oxyuris within the tissues of the genital organs. Claims of having observed this parasite in the lumen of the vagina,[75] cervix,[29] uterus [76] and tubes [32] had previously been published. Klee's patient was 59 years old and had had two small postmenopausal hemorrhages *per vaginam*, one a year and the other six weeks before hospitalization; since the second hemorrhage there had been a reddish yellow vaginal discharge. Examination showed superficial excoriation of the vulva and a tumor-like thickening of the posterior lip of the cervix, which bled easily when touched. The clinical diagnosis was carcinoma of the cervix. Biopsy showed a gravid threadworm surrounded by necrotic tissue at the center of an extensive inflammatory focus; further sections revealed a very early squamous carcinoma. Threadworms were found in the feces, and the patient gave a history of long-standing itching of the anus and vulva. Klee illustrated his report with a convincing drawing of the Oxyuris granuloma, but did not include one of the carcinoma. He considered the association of the carcinoma and the granuloma to be coincidental.

All the other records of intrinsic genital lesions associated with the presence of Oxyuris concern the fallopian tubes. Chiari [28] reviewed the available evidence for the pathogenicity of Oxyuris, and reported a case in which an oxyurid was found in a severely inflamed tube

73. Ash, J. E., and Spitz, S.: Pathology of Tropical Diseases, Philadelphia and London, W. B. Saunders Company, 1945, pp. 327-328.

74. Klee, F.: Zentralbl. f. Gynäk. **44**:939, 1920.

75. Spitzer.[27] Heller.[28]

76. Vix.[30] Leuckart.[31]

removed at operation from a patient aged 20 years who had right-sided acute suppurative salpingo-oophoritis. The worm, a gravid female, lay partly in a mucosal crypt, partly within the wall of the tube. Many embryo-containing ova were seen, surrounded by necrotic tissue. Eosinophil granulocytes were abundant in all parts of the tubal wall. Numerous lymphoid follicles with germinal centers had formed, and Chiari considered this significant because follicles are very well developed in the vermiform appendixes of children with oxyuriasis. For these reasons, and because no micro-organisms were found in smears of the fibrinopurulent serosal exudate or in sections (cultural examination was not possible), he believed that Oxyuris might alone have been responsible for the salpingitis. His arguments are not convincing: Failure to find bacteria in stained sections is not proof of their absence; it may, moreover, be doubted whether the appendical lymphoid follicles are better developed in children with oxyuriasis than in those without, and well formed follicles with Flemming centers are often seen in the fallopian tube in cases of active chronic salpingitis in which no question of a metazoan cause arises.

Jones and Bunting [77] reported the case of a 22 year old woman, operated on for appendicitis; the appendix was acutely inflamed and contained more than 20 live threadworms as well as several concretions; the left ovary and fallopian tube, which were densely adherent to the pelvic wall, were also removed. The lateral half of the tube contained an abscess 2.5 cm. in diameter. Serial sections of the thickened wall of the tube at this site showed a gravid oxyurid with a surrounding zone of necrosis containing many eosinophil granulocytes and enclosed by a connective tissue capsule. No relevant changes were found in the ovary or in endometrial curettings. The patient gave a ten year history of perineal itching.

Smith and Denton [78] described a case of pyosalpinx which they attributed to Oxyuris. The 23 year old patient was operated on for persistent lower abdominal pain; partial hysterectomy was performed, with resection of all the adnexa except the right ovary. Dense pelvic adhesions were present. The right tube had undergone torsion. There was a left-sided pyosalpinx, the contents of which were sterile. Histologically, the left tube showed severe chronic inflammation, with many foreign body giant cells. The puriform contents of the tube proved to be the "product of ischemic necrosis." Parasites, considered to be Oxyuris, were numerous in the inflamed tissues, and there was a definite foreign body reaction around them. No ova were found. Neither the descriptions of the worms nor the illustrations are altogether

77. Jones, W. J., and Bunting, C. H.: Arch. Path. **11**:229, 1931.

78. Smith, W. S., and Denton, J.: Am. J. Obst. & Gynec. **16**:205, 1928.

convincing, and some doubt may exist as to the identity of the parasites. No worms or ova were found in the feces.

Ku [79a] and Wu [79b] reported the case of a 30 year old Chinese woman with a history suggestive of gonorrhea, following which pain developed in the lower part of the abdomen, leading to hysterectomy, bilateral salpingectomy and left oophorectomy. Both tubes proved to be patent. A nodule, about 1 cm. in diameter, was found near the lateral end of the left tube; Ku [79a] described its situation as in the wall of the tube beside the lumen. Sections showed granulation tissue infiltrated by eosinophil granulocytes surrounding a large area of necrosis containing a gravid oxyurid; the photomicrograph is convincing. These authors also observed calcified material in the cortex of the left ovary, which they considered to represent ova of a parasite; the description and illustrations, however, suggest that these were not ova but calcific spheruloids such as are seen from time to time in this situation. Oxyuris was not found in the patient's stools, but Ascaris and hookworm ova were present. It is of interest to note that this woman had an old complete perineal tear, which may well have facilitated the parasite's invasion of the genital tract.

Chomet's [80] patient had received multiple gunshot wounds when aged 32; some involved the abdomen. She had recovered without operation and did not appear to have had any peritonitis. Some eighteen months later, the right ovary and fallopian tube were excised to relieve symptoms thought to be due to adnexal inflammation. Six months afterward the left adnexa were removed. The fimbrial end of the left tube was occluded by fibrosis; nearby there were a few firm nodules, 6 mm. in diameter. Sections showed diffuse chronic salpingitis. The nodules consisted of necrotic tissue containing many acicular crystals and numerous typical Oxyuris ova; a thin layer of fibrous tissue, infiltrated by chronic inflammatory cells, surrounded the nodules, and a few multinucleated giant cells were present in this fibrous capsule, the margin of which lay immediately deep to the mucosa. The appendix was normal, and there had been no evidence at operation that the bowel had been injured by the bullet wounds. Chomet considered that the ova had been deposited by a parasite which had migrated up the genital canal.

Strassen [81] found calcified masses in the wall of a fallopian tube of a woman aged 26, who had tuberculous peritonitis. The masses,

79. (*a*) Ku, D. Y.: Tr. Far East. A. Trop. Med. **1**:605, 1934. (*b*) Wu, L. C.: Chinese M. J. **49**:256, 1935.

80. Chomet, B.: Arch. Path. **34**:742, 1942.

81. Strassen, O. A.: Ueber den Befund von Oxyuris vermicularis im weiblichen Genitaltraktus mit einem neuen Fall aus dem pathologischen Institut zu Bonn, Inaugural Dissertation (Bonn), Bonn, H. Ludwig, 1915.

which occurred singly or in clumps, were surrounded by foreign body giant cells, and the adjacent tissues were fibrotic. According to Strassen, decalcification made it possible to identify these structures as Oxyuris ova, but the evidence is not convincing. It is more probable that they were spheruloids of the type not uncommonly present in cases of chronic granulomatous salpingitis; the concentrically lamellar structure of these spheruloids sometimes gives them a superficially ovum-like appearance when decalcified.

(*b*) Pelvic Peritoneal Lesions: The number of cases of pelvic peritoneal lesions containing Oxyuris or its ova so far reported is 16, to which 2 further cases are added in the present paper. With the exception of the lesions in Wegner's [82] case and in Cabot case 24071,[83] all were incidental findings at operation or necropsy, and of no serious significance. The details of these cases are best given in tabulated form (see table), but certain special points raised by the original authors are mentioned in the following paragraphs.

P. Schneider [84] noted that in his case the fibrous capsule was too old for the parasite to have reached the peritoneal cavity when the intestine was torn at operation five days before necropsy. He suggested that the worm must either have penetrated through the intact bowel wall or have traversed the genital tract before the tubes were closed by inflammation, presumably gonococcic, years earlier.

Hueter,[50a] in his report of a case of "intestinal coccidiosis," later recognized to be oxyuriasis, mentioned 2 other specimens in which he had found "coccidia" identical with those in the intestinal case. Both were pea-sized nodules, one from the mesentery (no clinical data available), the other an incidental finding in the pouch of Douglas at operation. Presumably, these also were cases in which Oxyuris ova had been misinterpreted as coccidia, but he does not refer to them in the amending report on the intestinal case.[50b]

Hendriock [85] described the nodules in his case as consisting of hyaline fibrous tissue, with the remains of a female ascarid (*Spulwurmweibchen*) at the center. "Numerous fertile ovula," some showing embryos clearly, were surrounded by remnants of the body wall of the worm. He said that some ova, lying in what he believed to be degenerating worm tissue, showed the "characteristic layered shell with its wavy albuminous covering." A similar appearance is shown by some Oxyuris ova in case 1 in the present paper (fig. 4). The

82. Wegner, H.: Peritonitis oxyurica mit Bekanntgabe eines akuten, klinische Erscheinungen machenden Falles, Inaugural Dissertation (Heidelberg), Walldorf bei Heidelberg, Friedrich Lamade, 1933.

83. Cabot Case 24071, New England J. Med. **218**:305, 1938.

84. Schneider, P.: Centralbl. f. Bakt. (Orig.) **36**:550, 1904.

85. Hendriock: Zentralbl. f. Gynäk. **50**:3274, 1926.

Case	Author	Age	Lesion Found at:	Lesions	Site	Size and Macroscopic Appearances	Author's Conclusion	Microscopic Observations in the Lesions: Worm in Lesion	Free Ova in Tissues	Criteria of Identification	Necrosis	Granulation Tissue	Eosinophil Granulocytes	Giant Cells	Fibrotic Capsule	Crystals	Other Morbid Changes Present	History of Helminthiasis	Helminthiasis Found When Lesion Recognized
1	Marro, G.: Arch. per le sc. med. **25**: 161, 1901; Giorn. d. r. Accad. di med. di Torino **7**: 251, 1901	34	Necropsy (dementia paralytica)	1	Fimbrial end of left fallopian tube	Little larger than a pea; whitish, with soft, yellowish center	Cyst containing Oxyuris ova	0	+	Ova identical with examples of Oxyuris ova available for comparison	+	0	0	0	+	Cholesterol	0	0	Nil
2	Chiari: Prag. med. Wchnschr. **27**: 227, 1902 Kolb, R.: Centralbl. f. Bakt. (Orig.) **31**: 268, 1902	42	Necropsy (secondary carcinoma in brain, following mastectomy for carcinoma of breast)	10	Pouch of Douglas	4-7 mm. long by 4-5 mm. Like grains of rice; some stalked, some sessile	Oxyuris nodules	+	0	Reconstruction by drawing serial sections and comparison with known Oxyuris and ova; ova 50 by 24 microns	0	+	0	+	0	0	0	0	Ascaris found in oesophagus
3*	P. Schneider [84]	36	Necropsy 5 days after hysterectomy for metritis and left pyosalpinx	1	Stump of suspensory ligament of left ovary	Hard nodular thickening of peritoneum, 2 cm. in diameter	Oxyuris nodule	+	+	Ova 49 by 22 microns; asymmetric, with clear, double-contoured shell; embryos in some ova	+	0	0	+	+	0	(a) Right tube removed when 21; (b) fatal peritonitis from injury to bowel at last operation	0	Nil
4	Strada, F.: Arch. per le sc. med. **31**: 418, 1907	60	Necropsy (pneumonia following ileostomy to relieve obstruction associated with a femoral hernia)	5	Pouch of Douglas	7-8 mm. long by 4-5 mm. thick; whitish; hard	Oxyuris nodules	+	0	Ova 50-52 microns long by 24-28 microns wide; asymmetric; double-contoured shell, granular contents	+	–	0	–	+	0	Ulceration of herniated ileum, but no old or recent perforation or peritonitis	0	Nil
5	Unterberger [87] (from Askanazy's pathologic collection)	0	0	1	Pelvic peritoneum	0	Oxyuris nodule	0	+	Not stated	+	–	0	0	0	0	0	0	0
6*	Hueter [38a]	34	Operation on uterus	1	Pouch of Douglas	Pea size	Coccidiosis	0	+	See text	+	+	0	+	+	0	0	0	0
7	Schröder, R.: Lehrbuch der Gynäkologie	0	0	1	Pelvic peritoneum	0	Oxyuris nodule	+	0	Not stated	0	0	0	0	+	0	0	0	0
8	für Studierende und Aerzte, Leipzig, F. C. W. Vogel, 1922, pp. 344-345	0	0	1	Pelvic peritoneum	0	Oxyuris nodule	+	0	Not stated	0	0	0	0	+	0	0	0	0
9*	Hendriock [35]	49	Operation to remove ovarian cyst	2 conjoined	Beneath serosa at side of uterus	Larger: size of cherry stone; smaller: size of hempseed. Surgical diagnosis: myoma	Ascaris nodules	+	+	See text	+	0	–	0	+	0	0	0	0

10	Butter, R.: Ueber Oxyureneier in einem Serosaknötchen des Douglassehen Raumes, Dissertation, Munich, Müller & Steinicke, 1929	0	Operation	1	Pouch of Douglas	Size of cherry stone, white. Surgical diagnosis: ? gland, ? malignant neoplasm	Oxyuris ova nodule	–	+	Elongated and oval double contoured structures	+	+	+	–	0	0	0	0	0
11*	Wegner [82]	19	Operation for symptoms suggesting acute appendicitis	?	Omento-vesical adhesion (? also multiple nodules in pouch of Douglas and serosa of uterus)	Inflammatory mass, size of a cherry, excised from omento-vesical adhesion	Peritonitis oxyurica	+	+	Appearances and measurements (not quoted) of ova	+	+	+	+	0	0	Localized abscess in adhesion	0	Ova (identity not stated) in feces
12	Borrmann: Zentralbl. f. allg. Path. u. path. Anat. **60**: 395, 1934	0	0	1	Serosa of fundus of uterus	Pea size	Oxyuris nodule	+	?	Gravid female worm, 5 by 2 mm., with ova, 50 by 25 microns; ova double-contoured	0	+	0	0	–	0	0	0	0
13*	Cabot case 24071 [83]	33	Operation for symptoms suggesting appendical abscess	Multiple (1 excised)	Serosa of fallopian tubes (and pelvic fossa ?)	One nodule excised: 0.75 cm. in diameter	Oxyuris infection of salpinx and pelvic peritoneum	–	+	Appearances of ova	0	+	0	0	–	0	Localized peritoneal abscess (sterile ?)	0	0
14	Froriep, E.: Zentralbl. f. Gynäk. **62**: 973, 1938	39	Operation for retroposed uterus	1	Medial third of vesico-uterine fold	Pea size, stalked, gray red	Oxyuris nodule	+	+	Appearances of worm and ova	+	+	+	+	+	Charcot-Leyden	0	–	0
15*	Valteris [84]	46	Operation for retroposed uterus	Multiple (1 excised)	Serosal surface of uterus	Pea size. Surgical diagnosis: ? tuberculosis	Oxyuris nodule	+	+	Ova 46-50 microns long by 20-25 microns wide; asymmetric; homogeneous shell, granular contents	+	+	0	0	+	0	Old second degree perineal tear	0	0
16*	Deeds [85]	26	Operation to remove benign ovarian neoplasm	1	Near medial end of left round ligament of uterus	8 mm. nodule	Oxyuris granuloma in a lymph node (see text)	+	+	Not clear	+	+	+	0	+	0	0	–	Nil
17*	Case 1 of this paper	44	Operation for retroposed uterus	1	Right mesosalpinx near uterus	Firm ovoid nodule, 1.1 by 1.1 by 0.8 cm.; grayish white, with soft yellowish center	Oxyuris nodule	+	+	Characteristic ova (see text)	+	+	+	+	+	See text	–	–	0
18*	Case 2 of this paper [86]	0	Operation	? several	Serosal surface of uterus	Firm, pea size	Oxyuris nodule	–	+	Characteristic ova	+	+	+	+	+	–	0	0	0

Key: Cases marked * are referred to in the text.
+ indicates that the feature concerned was described in the original report as present in the case.
– indicates that the feature concerned was mentioned in the original report as being absent.
0 indicates that there was no information about this feature in the original report.
* Case 9: Oxyuriasis and ascaridiasis for as long as the patient could remember.

size of Hendriock's worm excludes the possibility of its being, as he stated, a "mature fertilised Ascaris lumbricoides," and ova of A. lumbricoides do not contain embryos until some time after they have escaped from the host's body. On this evidence Hendriock's case appears, in fact, to have been an instance of Oxyuris granuloma.

The case described by Wegner [85] was that of a young woman who had had abdominal pains for five months before she was admitted to a hospital. Two days before admission pain became localized in the right iliac fossa and was intense. The physical signs were those of acute appendicitis. At operation the appendix was normal, as were the uterine adnexa. Numerous hard nodules, the size of a lentil to that of a pea, were present throughout the pouch of Douglas and on the left side of the uterus. The omentum was adherent to the fundus of the bladder, and at this site there was a cherry-sized inflammatory mass. When this adhesion was freed, an abscess was opened; the bladder wall was intact. A gravid oxyurid and free ova were found in the excised portion of inflamed omentum. No bacteria were seen in Gram-stained preparations, but no other bacteriologic examination appears to have been made. The lesion appears to have been an early granulomatous reaction to a threadworm which had reached the pelvic peritoneum, presumably through the genital tract. The nature of the nodules elsewhere on the pelvic serosa was not investigated.

There is some evidence that peritoneal oxyuriasis also caused the abscess found at operation in Cabot case 24071.[83] This patient had an eight day history of abdominal pain. A peritoneal abscess, medial to the cecum, was found and drained; cultures of the pus obtained at operation were sterile, and Staphylococcus aureus isolated at a later examination was considered a contaminant (?). A second operation, a few weeks later, showed an inflammatory mass in the pelvis, with nodules on the fallopian tube; the appendix, which was retrocecal, appeared normal, and histologic examination confirmed this. One tubal nodule, about 0.75 cm. in diameter, was excised, and the first pathologic report was tuberculosis. Later, ova were found in it, and, as the patient's occupation was to import and distribute various species of South African snails, schistosomiasis was considered, until further study proved the eggs to be those of Oxyuris. It was considered that the parasite had entered the abdominal cavity through the lumen of the genital tract.

Valteris [86] suggested that in his case Oxyuris might have passed through the rectal wall, injured in some way by the pressure on it of the retroflexed and retroverted uterus, which was thought to have been the cause of clinical symptoms of retarded defecation, although there

86. Valteris, K.: Medicina, Kaunas **21**:293, 1940.

does not appear to have been any organic lesion of the bowel. As in other cases of peritoneal oxyuriasis, it seems more likely that the parasite entered the abdominal cavity *per vias naturales*.

Deeds's [87] case is interesting because he thought that the lesion had developed in a lymph node. The only evidence for this was the presence of several discrete small collections of lymphocytes just beneath the capsule of the nodule. As lymphocytic infiltration and aggregation are commonly observed at the periphery of the Oxyuris granuloma, their presence in his specimen is not proof that it was a lymph node.

The only other report in the literature in which a lymph node has been said to be the site of an Oxyuris lesion is that of Kastranek,[88] and this also was probably a misinterpretation. Kastranek's patient was a woman aged 23, with symptoms suggesting acute appendicitis. At operation there was slight inflammation of the serosa of the cecum, but the appendix was normal. A 1 cm. "lymph node" in the ileocecal angle, 1.5 cm. from the bowel wall, was noticed and excised. Histologically, the appendix was normal. The "lymph node" consisted of lymphocytes, a connective tissue capsule and an abscess-like central cavity containing a fully developed "Oxyuris." Neither the sex of the parasite nor the presence of ova is mentioned, and there are no data or illustrations by which to judge its identification. If the parasite was Oxyuris it is probable that the lesion was a subserosal Oxyuris granuloma unrelated to any lymph node. The genital tract is a much more probable route for Oxyuris to take than that suggested by Kastranek, who postulated that one or more larvae passed through a defect in the bowel mucosa and along the lymphatic channels to reach a lymph node, where they matured.

(*c*) Other Peritoneal Lesions: In all the foregoing cases except Kastranek's doubtful one, which has just been dealt with for convenience, the Oxyuris nodules were found in the pelvic peritoneum, in close relationship with the uterus or its adnexa. In the following cases other parts of the peritoneum were involved.

Goodale and Krischner [89] reported the case of a 21 year old patient who had a ureterocolostomy performed because of a permanent vesicovaginal fistula following parturition. At the operation several loops of small intestine were seen to be studded with hard, white nodules, each slightly larger than a pea, and thought by the surgeon to be "tubercles." One was excised and proved to be a typical Oxyuris granuloma containing a gravid worm. Kaufmann [90] mentioned a some-

87. Deeds, D. D.: Am. J. Obst. & Gynec. **54**:890, 1947.

88. Kastranek, F.: Wien. klin. Wchnschr. **60**:51, 1948.

89. Goodale, R. H., and Krischner, H.: Arch. Path. **9**:631, 1930.

90. Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie für Studierende und Aerzte, ed. 7-8, Berlin and Leipzig, W. de Gruyter & Co., 1922, p. 672.

what similar case, that of a woman aged 31, who had had oxyuriasis for eight years when numerous nodules were found on the colon and mesocolon during an abdominal operation (reason for latter not stated); in the nodule examined Oxyuris ova were found in degenerating granulation tissue which was surrounded by a broad zone of infiltration of eosinophil granulocytes.

Fingerland and Maršálek [91] described the case of a woman of 49 who for four years had had a soft swelling in the right groin, painless except during the two menses preceding admission. At operation the swelling appeared as an egg-sized fibroma-like mass which was adherent to the inguinal ligament and to the processus vaginalis peritonaei. Apparently there was no hernia. In removing the mass it was necessary to resect part of the adherent peritoneum; the uterine adnexa were examined through the resulting aperture and found to be normal. When bisected, the specimen was seen to consist of a fibrous wall, 1.5 cm. thick, enclosing a hazel-nut-sized cavity lined by endometrium-like tissue and containing thick, dark brown fluid. Inguinal endometriosis [92] had been the preoperative diagnosis, and this seemed to be confirmed by the naked eye appearances, but histologic examination showed something else. The connective tissue capsule was infiltrated by lymphocytes and lined internally by partly necrotic granulation tissue. At one point in the latter scattered typical Oxyuris ova were found, with many eosinophil granulocytes; no worm was seen. The patient had had intestinal oxyuriasis for at least eight years, and worms were found in her stools after the operation. The authors assumed that a gravid oxyurid had traversed the genitalia and the peritoneal cavity to reach the inguinal canal along the processus vaginalis.

I know of only 2 other cases of Oxyuris granuloma recorded in the literature; in both the great omentum was involved, as it was also in the case of Wegner,[92] referred to under "Pelvic Peritoneal Lesions." Bodechtel [93] reported the case of a woman, aged 38, operated on for uterine retroflexion. During the operation, appendicectomy was performed, and a 3 cm. long adhesion, "as thick as a little finger," between the great omentum and the posterior wall of the uterus was resected. At the center of the adhesion there was a necrotic focus surrounded by granulation tissue and containing many characteristic threadworm ova; no other foreign bodies were present. The mucosa of the proximal half of the appendix was normal; the lumen of the distal half was obliterated by scar tissue, and a definite constriction separated the patent and occluded parts. At the tip the scar tissue filled a punched-out breach in the muscularis and projected mushroom-wise into the sub-

91. Fingerland, A., and Maršálek, J.: Časop. lék. česk. **80**:532, 1941.
92. Moloney, G. E.: Brit. M. J. **1**:435, 1949.
93. Bodechtel, G.: Zentralbl. f. Gynäk. **51**:1500, 1927.

serosa. Bodechtel suggested that an attack of appendicitis had caused the constriction and obliterated the lumen at that level; a subsequent attack led to perforation of the distal half, the contents of which, sterile by then, provoked only a local, aseptic peritonitis; the ova were shed into the peritoneal cavity at this time and were enveloped in a lappet of omentum. Bodechtel's argument is weakened because of the unlikelihood of a second attack of appendicitis causing perforation without infection and because of the absence from the patient's history of anything suggestive of even a mild local peritonitis. The reproductive tract seems a more likely passage way. The patient had had threadworms as a child; postoperative examinations of feces revealed no infestation.

F. Schneider's [94] patient, a woman of 27, had a history of repeated attacks of pain in the right lower abdominal quadrant. She was admitted in an acute attack of two days' duration, and laparotomy was performed. Abundant, greasy, turbid exudate was found, and two large cysts in the great omentum contained similar material. The affected omentum and the unaltered vermiform appendix were resected. The pelvic viscera appeared healthy. Examination of the specimens showed a patchy fibrinopurulent exudate on the surface of the omentum, adherent folds of which enclosed abscess-like cavities lined by granulation tissue. Elsewhere in the omentum there were many foreign body pseudotubercles containing typical threadworm ova. The appendix showed no changes other than a mild peritoneal reaction. Schneider concluded that the ova alone were responsible for the entire process, their "chemicotoxic" products provoking a severe inflammatory reaction, for the development of which he saw no need to incriminate hypothetic intestinal or vaginal bacteria accompanying the worm.

Comment.—In all these 23 previously reported peritoneal cases, with the possible exception of 5,[95] the result of Oxyuris invasion of the peritoneal cavity was of no clinical significance, the intruder being dealt with, as any bacteriologically sterile foreign body would be, by development of a sclerosing granulomatous reaction, walling it off.

There can be no doubt that the genital tract is the usual route by which the invading worm gains access to the peritoneum. In addition to the fact that threadworms or lesions caused by them have been observed in vagina, cervix, uterus and tubes, strong supporting evidence for this pathway is afforded by the facts that the peritoneal lesions so far reported have been found only in women and that only female worms or ova have been identified in the lesions, never male worms, which do not migrate to the perianal region.

94. Schneider, F.: Zentralbl. f. Chir. **58**:1301, 1931.

95. Wegner.[82] Cabot Case 24071.[83] Kastranek.[85] Fingerland and Maršálek.[91] Schneider.[94]

From the descriptions given by the authors named in the foregoing pages it is possible to define a relatively constant morphologic appearance of the nodules which form around oxyurids or their ova in the tissues. Macroscopically, they are usually a centimeter or rather less in their greatest dimension, firm, and whitish, with a yellowish center. Histologically, there is a capsule of more or less hyaline fibrous tissue, usually infiltrated by lymphocytes, which may form small groups or even follicles. Internal to this layer is a zone of granulation tissue surrounding a central necrotic area in which the parasite or its remains or only ova are seen. The ova appear to be considerably more resistant than the worm itself, and they remain well preserved when the latter is scarcely recognizable or has completely disappeared. Eosinophil granulocytes are often conspicuous in the cellular exudate, but may be absent. Foreign body giant cells may or may not be present in the granulation tissue zone, or about the worm or the ova. The few authors who mention bacterial staining saw no micro-organisms. Charcot-Leyden crystals are found occasionally, in cases in which there is a considerable aggregation of eosinophil granulocytes.

The peritoneal nodules are perhaps commoner than is realized, for as they usually cause no symptoms they are found only incidentally. Possibly many escape detection, being considered fibromatous or myomatous on naked eye inspection, without microscopic confirmation; the nature of others may be overlooked because the sections examined do not include parts of the worm or any ova.

REPORT OF CASES

CASE 1.—L. E., born Sept. 12, 1903, was admitted to Selly Oak Hospital, Birmingham, on June 11, 1947, with severe erosion and chronic inflammation of the cervix and retroflexion and retroversion of the uterus. Total hysterectomy and bilateral salpingo-oophorectomy were performed. No history of parasitic infestation was obtained. Feces and blood were not examined.

Specimen (fig. 1).—Apart from the patulous and eroded cervix, the uterus was normal for a parous woman of this age. The ovaries and tubes appeared normal. In the right mesosalpinx, immediately adjacent to the tube and 1.5 cm. lateral to the angle between it and the round ligament of the uterus, was a sessile, firm, grayish white, ovoid nodule, 1.1 by 1.1 by 0.8 cm.; the smooth, glistening serosa was reflected over its surface, the nodule jutting forward from the plane of the mesosalpinx. The cut surface of the nodule showed an outer rim of firm, translucent, grayish white tissue, 2 to 3 mm. thick, sharply demarcated from an irregular, grayish yellow central zone of softer consistency, the periphery of which formed a hair-fine, yellow margin between the two zones. The nodule was easily separated from the wall of the fallopian tube, which was not involved.

Histologic Observations.—The nodule was fixed *in situ* in formaldehyde-saline solution (4 per cent formaldehyde) and then divided into three portions by two parallel cuts, 1 mm. apart, at its broadest part; the central slice was left attached to the rest of the surgical specimen, which was preserved. When this slice was examined by strong transmitted light under the high power binocular dissecting

Fig. 1 (case 1).—Anterior aspect of the surgical specimen. The Oxyuris granuloma is indicated by an arrow. (1.12 × natural size.)

Fig. 2 (case 1).—Section of Oxyuris granuloma. The dark central area is the zone of necrosis, consisting of degenerating eosinophil granulocytes in a matrix of intensely hematoxyphil material. (Hematoxylin-eosin; × 7.)

microscope, no sign of any parasite was seen in the tissue. The two larger portions of the nodule were embedded in paraffin and examined in serial sections stained with hematoxylin and eosin (fig. 2). As required, these stains were removed from some sections, which were then restained by other methods.

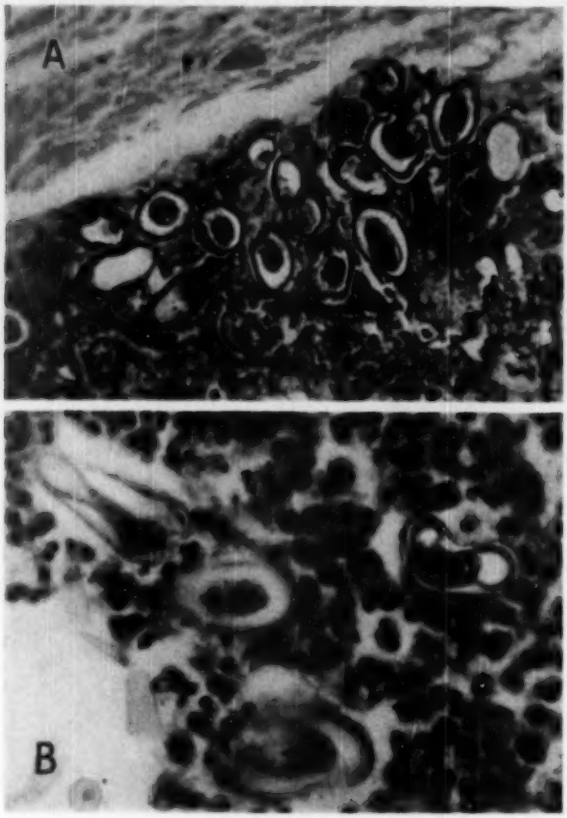


Fig. 3 (case 1).—*A*, Oxyuris ova at the margin of a necrotic zone. (Heidenhain's iron-hematoxylin and eosin; × 400.) *B*, distorted ova surrounded by degenerating eosinophil granulocytes. Note the group of Charcot-Leyden crystals in the lower left corner. (Hematoxylin-eosin; × 800.)

The subserosal connective tissue was loose in texture and contained many engorged capillaries; it was moderately heavily infiltrated by inflammatory cells, mostly eosinophil granulocytes. Deep to the subserosa was a zone of partially hyalinized scar tissue, corresponding with the rim of grayish white tissue seen

macroscopically. The interstices of this fibrous tissue were heavily infiltrated by lymphocytes and plasmacytes, with numerous eosinophil granulocytes and occasional small groups of neutrophil segmented granulocytes. The marginal area between the fibrotic capsule and the central part of the nodule had two zones, an

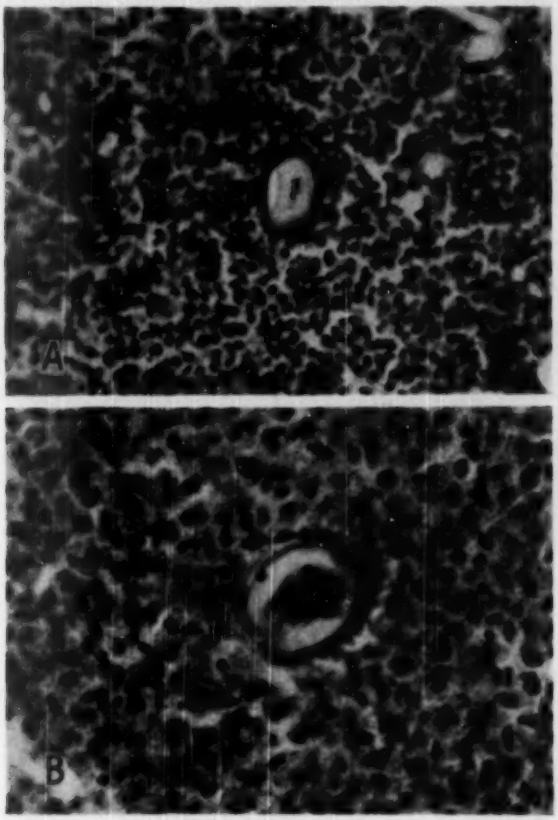


Fig. 4 (case 1).—*A*, Oxyuris ovum with a wavy homogeneous coating of eosinophil material giving it a superficial resemblance to an Ascaris ovum. (Hematoxylin-eosin; × 400.) *B*, Oxyuris ovum with an irregular deposit of hyaline material on its surface, reminiscent of the appearance of Ascaris ova in tissue sections. (Hematoxylin-eosin; × 800.)

outer of young fibrous tissue with heavy collections of lymphocytes and eosinophil granulocytes and an inner of loose-textured granulomatous tissue, consisting of epithelioid cells with occasional small multinucleated giant cells and only scanty

eosinophil granulocytes. The innermost cells of the latter zone were necrotic and merged into the central zone of necrosis. Here and there in the marginal area between the capsule and the necrotic center, small pseudotubercles had formed; they consisted of more or less radially arranged epithelioid cells, with occasional multi-

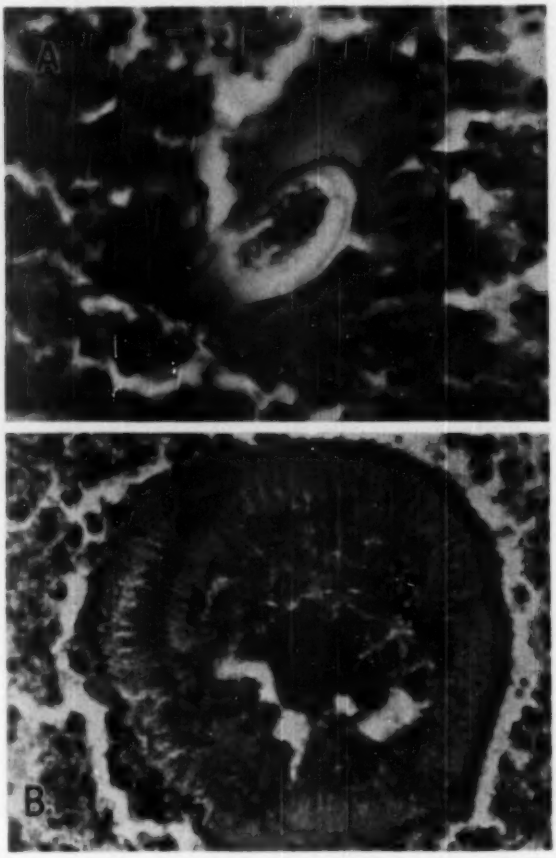


Fig. 5 (case 1).—*A*, Oxyuris ovum with a broad zone of hyaline material at its surface. (Hematoxylin-eosin; × 800.) *B*, cross-section of the tail of a threadworm (Oxyuris) surrounded by degenerating eosinophil granulocytes. (Hematoxylin-eosin; × 800.)

nucleated giant cells, and sometimes there was a narrow rim of fibrosis around them. Some of the giant cells had formed around amorphous eosinophil material, in which an occasional ovum was seen.

The necrotic center of the nodule consisted of a structureless mass of degenerating cells, separated by fine threads of intensely hematoxyphil material, apparently fibrin impregnated by chromatinic substance. Eosinophil granulocytes formed a considerable proportion of the identifiable degenerating cells. Scattered throughout the necrotic zone, and occasionally in the granulomatous tissue at its periphery, were ova of a parasite (fig. 3*A*); they were scanty in some sections, but in others as many as 50 could be found. Many of the ova were distorted (fig. 3*B*), and of some only the folded shell remained; others were well preserved and showed all the characteristics of Oxyuris ova. The shell was smooth and double-contoured; many ova lay in the tissues with the longer of their transverse axes in the plane of the section, showing the typical asymmetry, and the mean dimensions of 100 such ova were 50 by 29 microns (the mean dimensions of 200 segmenting ova seen in the same plane in gravid threadworms in a vermiform appendix, fixed and processed by the same methods, were found to be 54 by 29 microns). In many ova the characteristic chromatin aggregates of the later stages of segmentation were seen; no definitely recognizable embryos were found. Occasionally there was seen a fine, intensely hematoxyphil outline to the outer surface of the shell. Other ova were surrounded by an irregular, granular layer of eosinophil refractile material which stained deep blue with phosphotungstic acid hematoxylin (figs. 4 and 5*A*).

In some sections, fragments of eosinophil homogeneous material were seen, possibly parts of the chitinoid cuticle of a grown parasite. They were surrounded by the necrotic material, and structural detail was difficult to identify. Part of the tail of a worm could, however, be seen, including a cross section (108 microns in diameter) in which the finely scalloped cuticle could be identified surrounding the remains of the four somatic muscle masses, in which the peripheral radial striation could be recognized (fig. 5*B*).

No other foreign bodies were seen. No bacteria were found in Gram or Ziehl-Neelsen preparations.

Many crystals were present in the necrotic areas (fig. 6). The majority were elongated and lancet shaped, in the characteristic fashion of Charcot-Leyden crystals; their length varied from 5 to 200 microns, but most were of the order of 25 microns long. A few of the crystals appeared as hexagons, as Charcot-Leyden crystals do when cut in cross section.[96] The crystals were colorless or faintly yellow when unstained; they were strongly acid-fast by the Ziehl-Neelsen technic, and they gave the same staining reactions as the Charcot-Leyden crystals studied by Ayres and Starkey,[97] except that frozen sections were not available for sudan-staining; they did not stain metachromatically with toluidine blue or show any elective affinity for polysaccharide stains, nor were they stained by so-called elastin stains; contrary to Hueter's[50a] finding, no gram-positive particles were demonstrable in them; they did not give Feulgen's "plasmal" reaction, a point of some interest in relation to the opinion expressed by Ayres and Starkey[97] that Charcot-Leyden crystals are formed from the nuclei of eosinophil granulocytes. The crystals behaved in polarized light in a fashion similar to that described by the latter authors.

CASE 2.[98]—No history is available in this case except that a number of small nodules on the serosal surface of the uterus were noticed at operation; one was

96. Ayres, W. W.: Blood **4**:595, 1949.

97. Ayres, W. W., and Starkey, N. M.: Blood **5**:254, 1950.

98. The specimen is from the histologic collection of Dr. A. H. T. Robb-Smith, Oxford, England.

removed for examination. The preparation available was a paraffin section, stained with hematoxylin and eosin, of a granuloma (6 by 4 mm.). The lesion consisted of an outer zone of dense fibrous tissue surrounding a central area of necrosis in which a very small number of typical Oxyuris ova were present. The appearances were similar to those in case 1, but eosinophil granulocytes were fewer; no trace of the worm itself was found, and no crystals were seen.

Case 3.—P. M.,[99] a boy, was born Feb. 2, 1936. His birth was normal, and he developed normally. His general health was good. Apart from the conditions to which the present report is relevant, he had no illnesses except pertussis, measles and chickenpox, and the course of these was uncomplicated. He was circumcised in infancy. His family was healthy, and there was no family history of worm infestation.

History.—When aged 3 years he had an abscess in the left loin, which appears to have attracted attention solely because of local symptoms; there was no urinary

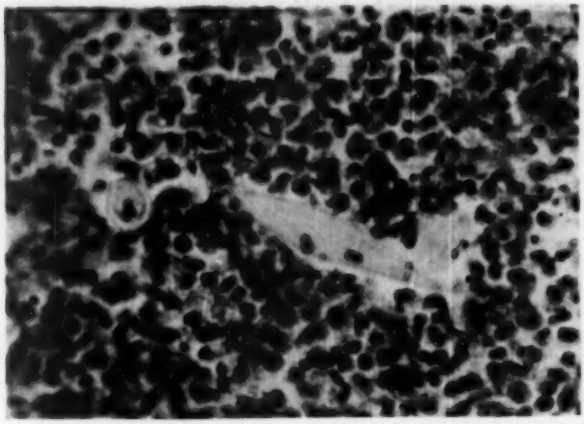


Fig. 6 (case 1).—Charcot-Leyden crystals in the cellular exudate in the necrotic zone. One crystal, cut across its long axis, appears hexagonal. (Hematoxylin-eosin; × 640.)

disorder. The abscess was incised. Ten years later he had another abscess in the left loin, causing local swelling and pain; a few days later it was incised; examination of the pus is said to have been "negative." This incision healed for only a few days and was then followed by a persistent sinus. A radiopaque calculus was demonstrated in the left renal area, and on intravenous pyelography there was no evidence of excretion on the left side (fig. 7). He was admitted to the Queen Elizabeth Hospital, Birmingham, on Nov. 16, 1949, four months after the second abscess had developed. He had no urinary symptoms, his bowels acted naturally, and his weight was increasing normally.

Examination.—He was a well developed child of good physique, and he looked well. His mouth and pharynx were healthy. No abnormality was found in the

99. United Birmingham Hospitals reg. no. C.88473.

nervous, respiratory or cardiovascular systems. His arterial blood pressure was 130 mm. of mercury systolic and 70 diastolic. The right kidney was just palpable; abdominal examination was otherwise without noteworthy findings. The genitalia were normal. Over the iliac crest in the left loin there was a small sinus, from which a little exudate escaped; the skin around it was healthy.

Special Investigations.—November 17: The urine contained no protein or reducing substance; its specific gravity was 1.024; the centrifugate contained no cells, casts, crystals or micro-organisms; cultures yielded only a scanty growth of

Fig. 7 (case 3).—Intravenous pyelogram: Normal excretion on the right side; no excretion on the left. The small, irregular shadow in the left renal area, opposite the tip of the transverse process of the third lumbar vertebra, is the calculus found in the kidney remnant after nephrectomy.

coliform bacteria. A urea concentration test gave a normal result. The blood urea amounted to 37 mg. per hundred cubic centimeters. The erythrocyte count was 5,320,000 per cubic millimeter; hemoglobin content was 14.7 Gm. per hundred cubic centimeters; the leukocyte count was 5,800 per cubic millimeter, with a normal differential count.

November 18: Midstream urine contained moderate numbers of pus cells, but no erythrocytes, epithelial cells, casts or crystals; no bacteria were seen in smears; cultures yielded a moderate growth of Proteus morgani and paracolon bacilli.

Operation (November 19).—The region of the left kidney was explored through a posterolateral incision. A fibrofatty mass containing a calculus and the remnant of the kidney was excised; the colon was very adherent to this tissue. The sinus in the loin was curetted, its track being found to extend to the renal bed. The wound was closed, with a tube drain in place.

Postoperative progress was satisfactory. The nephrectomy wound discharged a little pus for a few days, but healed within two weeks. The sinus in the loin closed rapidly after the curettage. When seen five months after the operation the boy was in excellent health.

After examination of the surgical specimen had shown the presence of Oxyuris, the stools were examined; gravid female threadworms and free embryo-containing threadworm ova were found in them. It now transpired that three years previously persistent scratching at the anal region had attracted attention and been found to be due to the presence of threadworms; the child was given several courses of treatment consisting of quassia enemas followed by diphenan (parabenzylphenyl carbamate) by mouth. Symptomatic recovery resulted, and no more worms were seen. The matter was forgotten until the unexpected findings in the resected kidney brought it back to mind.

Specimen.—The specimen (5.2 by 3.8 by 3.8 cm.) consisted of fatty tissue, at the center of which was a firm, whitish, fibrous mass (2.8 by 2.4 by 1.7 cm.), which bore no resemblance to a kidney except in the presence of an ill defined hilus at one margin. The hilar blood vessels were very narrow and their walls thickened; their caliber was not more than 1.5 mm. The stump of the ureter, 7 mm. long, was 3 mm. in diameter, and its lumen admitted a probe of not more than 0.7 mm. in diameter. It was impossible to define the pelvis by dissection, the ureteral stem disappearing into the fibrotic tissue. A rather sharply outlined focus (6 by 4 by 4 mm.) of caseous appearance and consistency was separated from the hilus by a zone of fibrous tissue, 2 to 4 mm. wide; smaller, similar foci of necrosis were present here and there throughout the central fibrotic mass.

In the middle of the fibrotic area there was an irregular, slightly rough, brittle calculus, weighing 690 mg.; a small fragment was examined chemically and found to contain calcium, magnesium, ammonia and phosphate, with some carbonate and no uric acid. The rest of the stone was demineralized in a 5 per cent solution of formic acid, embedded in paraffin and sectioned; it showed no recognizable structure and nothing of parasitic nature.

Histologic Observations.—The tissue was fixed in formaldehyde-saline solution (4 per cent formaldehyde). Numerous paraffin blocks were prepared, representative of every part of the specimen. Serial sections of the macroscopically necrotic areas were examined, and sections were cut at several levels in all the other blocks. Most sections were stained with hemalum and eosin; other staining methods were used as required. When more than two or three foci of calcification were found in sections of any block, further sections were examined, either after decalcification and reembedding of the block of tissue or by microscopically controlled decalcification of the sections themselves.

The periphery of the specimen consisted of normal adipose tissue, which merged through a fibroadipose zone into the fibrotic central area forming the greater part of the specimen. This central area consisted of a broad outer zone of very dense, hyaline scar tissue enclosing the surviving kidney tissue. The latter was represented by small groups of renal tubules lying in a moderately fibrous stroma (fig. 8*A*). The stroma was uniformly and heavily infiltrated by lymphocytes, along with occasional plasmacytes, eosinophil granulocytes and macrophages. Well developed lymphoid follicles, with Flemming centers, were present, particularly at

the periphery. Many of the renal tubules were dilated, and others were atrophic; many were filled with protein coagulum. No glomeruli could be identified. There were small groups of small blood vessels with very narrow or obliterated lumens

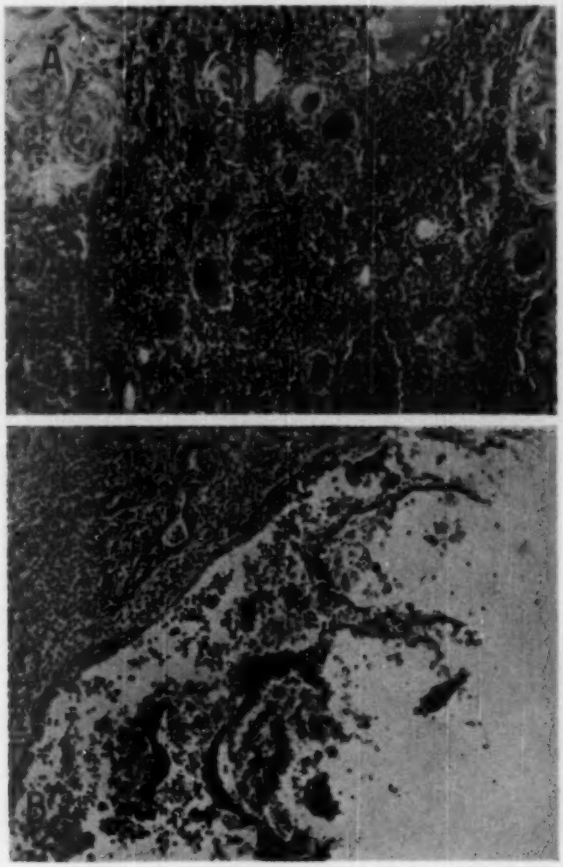


Fig. 8 (case 3).—*A*, surviving renal tubules containing colloid-like material and widely separated by a cellular infiltrate. (Hemalum-eosin; × 164.) *B*, remnants of a female oxyurid in the ureter. Near the lower center a lateral cuticular crest can be seen. (Hemalum-eosin; × 100.)

and greatly thickened, fibrotic walls, sometimes patchily hyalinized. The elastic laminas of the larger of the vessels were considerably increased in width and complexity.

The wall of what remained of the calices and ureter was atrophied and fibrotic, particularly where the calculus had been present. The mucosa and submucosa of the stem of the ureter were heavily infiltrated by eosinophil granulocytes, with some plasmacytes and lymphocytes; lymphoid follicles had formed in the deeper

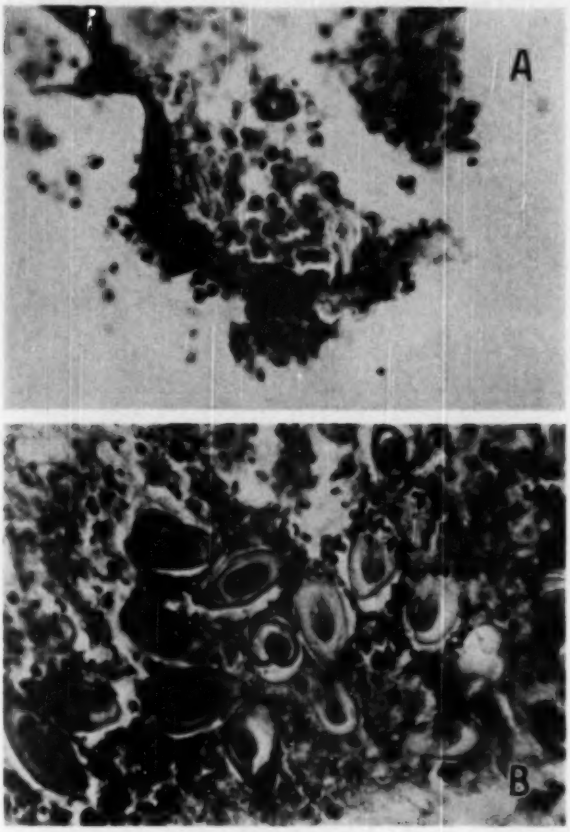


Fig. 9 (case 3).—*A*, higher magnification of a part of the field shown in figure 8*B*. An ovum is seen adherent to the body wall of the worm, and there is a typical Charcot-Leyden crystal among the degenerating eosinophil granulocytes. (Hemalum-eosin; × 400.) *B*, group of Oxyuris ova in a necrotic focus. (Hematoxylin-eosin; × 400.)

parts. The atrophic epithelium of the ureter was of transitional cell type; many eosinophil granulocytes had infiltrated between the epithelial cells. In its lumen were the remains of a female oxyurid (fig. 8*B*), identified by the chitinoid cuticle,

with its lateral crests, and by the presence of an occasional characteristic ovum, still adherent to the wall of the uterus (fig. 9*A*); the body cavity and the uterus had been invaded by eosinophil granulocytes and by macrophages, some multinucleated.

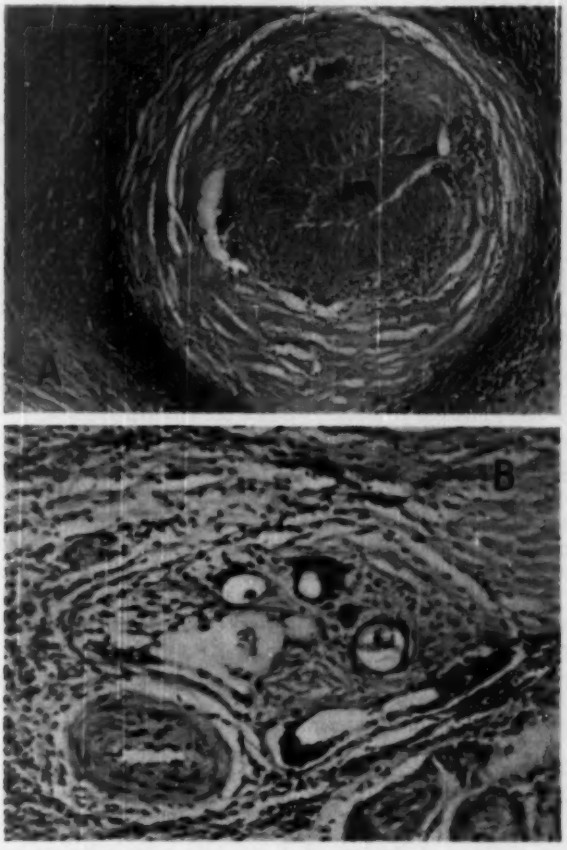


Fig. 10 (case 3).—*A*, sclerotic pseudotubercle with necrotic center and scattered multinucleated giant cells. (Hematoxylin-eosin; × 100.) *B*, foreign body giant cells surrounding homogeneous structures resembling the shells of Oxyuris ova. (Hematoxylin-eosin preparation of a decalcified paraffin section; × 200.)

The macroscopically necrotic foci in the kidney remnant were histologically identical with the necrotic areas in case 1, except that eosinophil granulocytes were very much less numerous than in the latter. The same granulomatous

boundary zone was present, with its sclerotic rim. Many ova were seen, some greatly distorted but many well preserved (fig. 9*B*); those in which the contents were recognizable showed the late segmentation stages of development; no embryonic larvae were seen. The mean dimensions of 50 well preserved ova were 56 by 27 microns. No adult parasites were found in the necrotic foci. Occasional Charcot-Leyden crystals were seen, a few of them cut across and appearing hexagonal; the crystals gave the same staining reactions as those in case 1.

Scattered in the vicinity of the necrotic foci there were sclerotic pseudotubercles, in most of which foreign body giant cells were present (fig. 10*A*). Some of the smaller of these granulomas had each developed around a single, uncalcified, identifiable ovum. Others enclosed round or ovoid calcified bodies, usually formed of multiple concentric lamellas and measuring between 40 and 250 microns in their longest axis. No ova or other formed structures could be identified with certainty in these calcific masses, even after decalcification, but now and again a smooth, homogeneous, curved body, resembling the shell of an Oxyuris ovum, remained in the smaller masses after decalcification (fig. 10*B*).

Gram and Ziehl-Neelsen preparations were made from every block, but no bacteria were found.

Comment.—It must be emphasized that no sign of the parasite or its ova was seen in the routine sections first examined in this case. The presence of tuberculoid granulomatous tissue and of an unusual number of eosinophil granulocytes attracted attention and led to examination of further sections, cut more deeply in the original blocks; in these, ova were found in the necrotic foci, and the parasite was encountered in the ureter.

COMMENT ON CASES

The pathologic observations made in cases 1 and 2 correspond well with those described by other authors in their accounts of peritoneal Oxyuris granulomas. It seems reasonable to assume that the granuloma in the mesosalpinx in case 1 formed around a gravid threadworm which had died in the pelvic cavity after migrating through the genital tract. It is of interest that, while the worm itself had almost completely disappeared, its ova were more resistant and remained well preserved; this observation applies also to case 3, and was made likewise in several of the previously published cases.

Case 3 appears to be unique; no record has been found in the literature of the presence in the ureter or the kidney of threadworms or their ova. The clinical history and pathologic observations pose two main questions: Was the renal condition wholly due to the presence of the parasite, and what was the route by which the latter invaded the kidney?

So far as it is possible to judge from the history, it seems likely that the abscesses at the ages of 3 and 13½ years were perinephric. There is no clue as to their pathogenesis. No urinary symptoms were observed at any time. The child was first found to have oxyuriasis seven years after the first abscess, and anthelmintic treatment given then resulted in symptomatic relief, which has persisted; nevertheless, threadworms and ova were found in his feces after the nephrectomy, more than three and a half years after symptomatic cure of the infestation.

It is impossible to say whether the left kidney was ever normal. It is possible that it was hypoplastic, and suffered further damage in the pyogenic infections to which such a congenital abnormality might have predisposed it. The boy had no other recognizable congenital defects, nor was there any family history of congenital disease, abnormal pregnancies or the like. His right kidney appears to have been normal. It may be that the extensive destruction of renal tissue resulted directly from the suppurative process which led to the development of the first perinephric abscess; alternatively, atrophy of the kidney and predisposition to further infection may have resulted indirectly, from occlusion of the ureter by formation of the stone found in the contracted pelvis.

The finding of a female oxyurid in the uppermost part of the stem of the ureter suggests at first sight that the parasite ascended the urinary tract. It is, however, more difficult to conceive a threadworm making its way against the urinary flow along the urethra and through the bladder to a ureteric orifice than to accept the possibility that it can pass through the female genital tract. In the present case other routes suggest themselves. At nephrectomy, the descending colon was observed to be adherent to the renal remnant; this was probably a result of the attacks of perinephritis; there is little reason to postulate a worm's penetration of the bowel wall either as the cause of the perinephritis or as the mode by which already diseased renal tissue became the site of a superimposed metazoan infestation, e. g., if the perinephric abscess had perforated into the lumen of the bowel. The other possibility is the sinus in the left loin, which followed incision of the abscess four months before nephrectomy and which opened by a small orifice on the skin surface just above the iliac crest. A gravid threadworm, wandering from the anus, could have entered this orifice and so reached the renal bed. That it could thus have reached the ureteral lumen cannot be proved, as it was not discovered at operation whether the sinus communicated with the ureter. Alternatively, although there was no pruritus around the sinus, the child may have conveyed ova on his fingers from the anus to the sinus; as the parasite found in the ureter was a gravid female, and as the ova in the necrotic foci were fertile, this method of infection would require not only maturation of larvae hatched from the contaminating ova but completion of the cycle in the affected tissues by conjugation of the sexes.

Which of these routes was the one followed cannot be said with certainty, but that an adult worm migrated from the anus to the skin sinus seems the most reasonable. Melchior's [72] case probably developed in this way. Study of future cases of urinary tract oxyuriasis and of Oxyuris infestation of sinuses will perhaps throw some light on the problem.

CONCLUSIONS

1. Threadworms seldom cause more than the local symptoms which result when the female parasites migrate nocturnally to deposit their eggs on the perianal skin.

2. Oxyuriasis is occasionally associated with ulcerative lesions of the small and large intestines, but the association is probably coincidental. The same is almost certainly true of perianal abscesses containing the parasites, which gain access to the already formed abscess cavities along sinuses.

3. Occasionally a dead immature oxyurid is found in the lymphoid tissue of the intestinal mucosa, surrounded by a low grade inflammatory reaction or by a zone of fibrosis. However, in most cases in which immature or adult parasites or the ova are seen in the tissues, there is no unequivocal sign of vital reaction to suggest that the affected tissues were still living when invasion occurred.

4. Oxyuris is not a significant cause of appendicitis.

5. Oxyuris only exceptionally causes pathologic changes in the tissues, its pathogenicity in this respect being trivial; nevertheless, it can, on rare occasions, alone produce such changes, and a more definite stand must be taken on this subject than that of such authors as Lane [100] and Napier.[101]

6. In a small number of cases, oxyurid-containing nodules have been found in the female genitalia or in the peritoneum. In every case of peritoneal involvement the patient was a woman. The parasite reaches the peritoneal cavity through the lumen of the genital tract. In a few such cases the presence of the parasite or its ova appears to have caused sufficient reaction to produce symptoms and lead to surgical intervention, but in the great majority the lesions have been incidental findings which cannot be correlated with any event in the patient's history.

7. In the differential diagnosis of Oxyuris granuloma the lesions have been thought on macroscopic examination to be tuberculous, occasionally leiomyomatous or fibromatous, schistosomal [28] or endometriotic.[91] Microscopically, they must be differentiated from other granulomas, e. g., those resulting from the presence of other parasites (notably the so-called pentastome larvae of the endoparasitic arthropod Linguatula rhinaria [serrata][102]) or of foreign bodies, tuberculosis, etc. When ova are seen they may be misinterpreted, e. g., as ova of schistosomes [103] or

100. Lane, C.: Lancet **2**:511, 1944.

101. Napier, L. E.: The Principles and Practice of Tropical Medicine, New York, The Macmillan Company, 1946, pp. 601-602.

102. Symmers, W. St., C., and Valteris, K.: J. Clin. Path., August 1950.

103. Fitzwilliams.[60] Cabot case 24071.[53]

of A. lumbricoides,[83] or as coccidia.[84] Conversely, some workers seem to have mistaken calcific spheruloids in the ovary [79] and tube [81] for Oxyuris ova.

8. In any granulomatous lesion of uncertain nature, particularly when it is associated with an unusually heavy mobilization of eosinophil granulocytes, numerous sections should be examined to insure that a metazoan parasite causing the condition is not overlooked. Chiari [28] stressed the fact that he chanced on the parasite in the first section of the affected tube examined and that he might otherwise easily have missed it; Fingerland and Maršálek [81] drew attention to a similar point. In the case reported by Jones and Bunting [77] the first sections suggested tuberculosis; the true nature of the condition was appreciated only when ova and parasites were found in serial sections prepared in order to try to confirm the etiologic suggestions. There was a similar experience in case 3 of the present paper.

9. Most of the observers who have described cases in the literature did not give wholly adequate evidence of the criteria by which the parasites or ova found were identified. If necessary, serial sections must be examined until morphologic features can be recognized with certainty; in this respect, the thornlike crest projecting on each side from the cuticle of Oxyuris when the worm is cut across its length is characteristic. Identification of ova must rest mainly on micrometric examination and the presence of any other diagnostic characteristics, such as the asymmetry of Oxyuris ova when they are viewed in certain planes, the spines of Schistosoma ova and the biterminal "caps" of Trichuris ova. Ova of A. lumbricoides may be identified by their peculiar, irregularly mammillated outer coat, but care must be taken not to confuse this feature of Ascaris eggs with the irregular albuminoid coating which may cover the surface of Oxyuris ova in inflammatory exudates.

SUMMARY

After an account of the biology of Oxyuris vermicularis (Enterobius vermicularis) and of some recent advances in knowledge of oxyuriasis, the published records of cases in which pathologic changes in the tissues have been attributed to the presence of Oxyuris or its ova are reviewed. Sclerotic granulomas of the pelvic peritoneum of women account for most of the cases in which this parasite or its ova undoubtedly caused the lesions in which they were found. The lesions were of clinical importance in only a small proportion of the cases.

Three new cases of Oxyuris granuloma are reported. The lesion in each of the first 2 cases was a characteristic peritoneal Oxyuris granuloma, an incidental finding in the mesosalpinx in one case and in the uterine subserosa in the other. In the third case, nephrectomy

was performed in a boy aged 13½ years, who had a chronic sinus in one loin following incision of a perinephric abscess: The remains of a gravid oxyurid were found in the ureter of the atrophic kidney, which itself contained necrotic foci in which the typical ova were found. This appears to be the first record of the presence of this parasite in the kidney or the ureter.

Mr. L. M. Park and Mr. Hugh Donovan gave permission to publish cases 1 and 3, respectively. Dr. Keith S. Thompson supplied the preserved specimen from case 1, which was originally diagnosed by him. Dr. A. H. T. Robb-Smith supplied the section from case 2.

Prof. Giovanni Marro, of Turin, Italy, Dr. Eugenio Bonetti, of Rome, Italy, and Dr. Douglas Symmers, of New York, provided copies of a number of early papers not accessible in England.

News and Notes

Meeting of the Histochemical Society.—The next meeting of the Histochemical Society will be held in Detroit on March 19 and 20, 1951, preceding the annual session of the American Association of Anatomists.

Deaths.—Roy Rachford Kracke, of Birmingham, Ala., dean and professor of clinical medicine (hematology) at the Medical College of Alabama and formerly professor and chairman of the department of pathology, bacteriology and laboratory medicine at the Emory University School of Medicine, Atlanta, Ga., died June 27, aged 53, of myocardial infarction. A specialist certified by the American Board of Pathology, he was chairman of the Section on Pathology and Physiology of the American Medical Association in 1937-1938, past president of the American Society of Clinical Pathologists, formerly vice president of the Georgia Association of Pathologists, member of the board of medical consultants in Oak Ridge, Tenn., member of the hematology study section of the United States Public Health Service and vice chairman of the medical advisory group of the Veterans Administration. He was joint editor of "Textbook of Clinical Pathology," joint author of "Diseases of the Blood and Atlas of Hematology," author of "Color Atlas of Hematology" and an associate editor of *Blood: The Journal of Hematology.*

James Way Denton, of New Rochelle, N. Y., director of pathologic laboratories and member of the medical boards at Lawrence Hospital in Bronxville, N. Y., and at New Rochelle Hospital, at various times affiliated with Bellevue Hospital in New York, White Plains (N. Y.) Hospital, Dobbs Ferry (N. Y.) Hospital, Tarrytown (N. Y.) Hospital and Sing Sing Prison Hospital in Ossining, and formerly assistant professor of pathology at Cornell University Medical College in New York, died June 16, aged 72, of cor pulmonale. He was a member of the College of American Pathologists and the American Medical Association, and was a specialist certified by the American Board of Pathology.

CORRECTION

In the August 1950 issue of the ARCHIVES lines were transposed near the bottom of page 177, in the article on "Crystalline Ester Cholesterol and Adult Cortical Renal Tumors" by Dr. Timothy Leary. The sentence beginning on the fourth line from the end of that page and the following sentence should read: "The degree of malignancy manifested in some human renal adenocarcinomas may be very high in places, together with contrasting fields that leave no doubt that the tumor had its origin from a papillary cystadenoma. The possibility that a simple papillary adenoma changes to a cancerous new growth when a miniature renal tumor reaches a diameter of 4 cm. suggests the influence of a more active carcinogen than unchanged cholesterol."

Books Received

THROMBOSIS IN ARTERIOSCLEROSIS OF THE LOWER EXTREMITIES. By Edward A. Edwards, M.D., specialist, certified by the American Board of Surgery; clinical associate in anatomy, Harvard Medical School; instructor in surgery, Tufts College Medical School; consultant in peripheral vascular disease, Joseph H. Pratt Diagnostic Hospital and Hospital of the Massachusetts Soldiers' Home; chief of vascular clinic, Boston Dispensary. Pp. 74, with 33 illustrations. Price $2. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1950.

This is an attractively published, short, informative, well written monograph on the importance of thrombosis in arteriosclerotic ischemia of the lower extremities. The study is based on correlation of clinical data and pathologic observations. The point is stressed that severe disability and other symptoms, related to marked ischemic changes, are due to the superimposed thrombosis. Sections are also devoted to treatment and illustrative case reports.

COLLECTED PAPERS OF THE MAYO CLINIC AND THE MAYO FOUNDATION. Edited by Richard M. Hewitt, M.D., A. V. Nevling, M.D., John R. Miner, Sc.D., James R. Eckman, Ph.D., M. Katharine Smith, B.A., Carl M. Gambill, M.D., M. P.H., and Florence Schmidt, B.S.E. Pp. 820, with 128 illustrations. W. B. Saunders Company, 218 W. Washington Square, Philadelphia 5, and 7 Grape St., Shaftesbury Ave., London, W.C. 2, 1950.

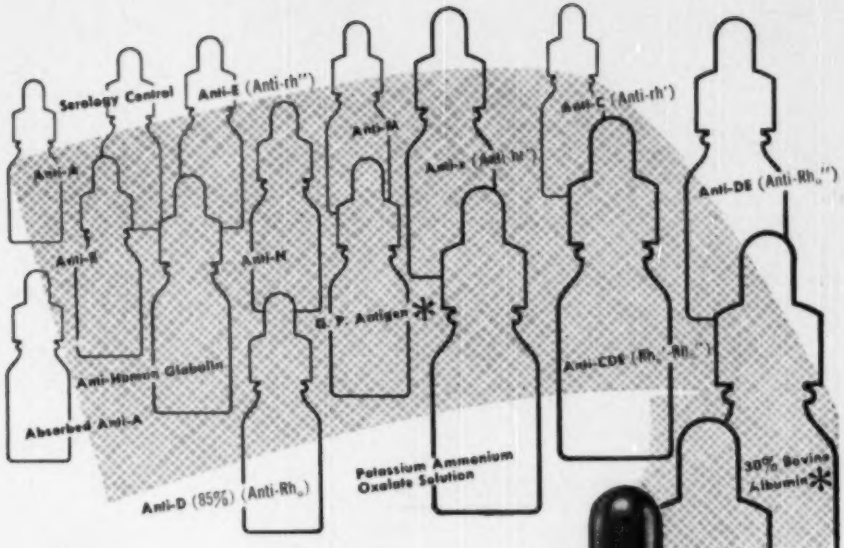
SIMMOND'S DISEASE—EXTREME INSUFFICIENCY OF THE ADENOHYPOPHYSIS. By R. F. Farquharson, M.B., F.R.C.P.(C)., professor of medicine and head of the department, University of Toronto; physician in chief, Toronto General Hospital, Toronto, Canada. Pp. 93, with 5 illustrations and 7 tables. Price $2. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1950.

PRINCIPLES OF HUMAN GENETICS. By Curt Stern, University of California, Berkeley. Pp. 628, with 198 illustrations. Price $7.50. W. H. Freeman & Company, 549 Market St., San Francisco 5, 1949.

CHEMOTHERAPIE DER TUBERKULOSE MIT DEN THIOSEMIKARBAZONEN. By Gerhard Domagk. Pp. 405, with 252 illustrations. Price $14.30. Georg Thieme Verlag, Diemershaldenstrasse 47, Stuttgart-O, 1950.

ANGINA PECTORIS AND MYOCARDIAL INFARCTION: WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM. By Heymen R. Miller, M.D., formerly principal physician and chief of the Signal Corps Climatic Research; attending physician, Sydenham Hospital; assistant professor of medicine, New York Postgraduate Medical School and Hospital; associate attending physician, Montefiore Hospital. Pp. 336, with 63 illustrations. Price $8.75. Grune and Stratton, Inc., 381 Fourth Ave., New York 16, 1950.

CURRENT THERAPY 1950: LATEST APPROVED METHODS OF TREATMENT FOR THE PRACTICING PHYSICIAN. By Howard F. Conn, M.D. Consulting Editors: M. Edward Davis, Vincent J. Derbes, Garfield G. Duncan, Hugh J. Jewett, William J. Kerr, Perrin H. Long, H. Houston Merritt, Paul A. O'Leary, Walter L. Palmer, Hobert A. Reimann, Cyris C. Sturgis, Robert H. Williams. Pp. 736. Price $10. W. B. Saunders Company, 218 W. Washington Square, Philadelphia 5, and 7 Grape St., London, W.C. 2, 1950.



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